PB86-242864

Airborne Asbestos Health Assessment Update

(U.S.) Environmental Protection Agency
Research Triangle Park, NC

Jun 86

U.S. Department of Commerce
National Technical Information Service
NTIS

United States
Environmental Protection
Agency

Office of Health and
Environmental Assessment
Washington DC 20460

EPA/600/8-84/003F
June 1986

Research and Development

PB86-242864

EPA

Airborne Asbestos Health Assessment Update

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA/600/8-84/003F	**2.**	**3. RECIPIENT'S ACCESSION NO.**
4. TITLE AND SUBTITLE Airborne Asbestos Health Assessment Update		**5. REPORT DATE** June 1986
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) See List of Authors, Contributors, and Reviewers		**8. PERFORMING ORGANIZATION REPORT NO.**
9. PERFORMING ORGANIZATION NAME AND ADDRESS		**10. PROGRAM ELEMENT NO.**
		11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Health and Environmental Assessment Office of Research and Development U.S. Environmental Protection Agency Research Triangle Park, N.C. 27711		**13. TYPE OF REPORT AND PERIOD COVERED** Final
		14. SPONSORING AGENCY CODE EPA/600/23

15. SUPPLEMENTARY NOTES

16. ABSTRACT

Recent data from population studies strengthened the association of asbestos with disease. Lung cancer and mesothelioma are the most important asbestos-related causes of death. The data suggest that the excess risk of lung cancer from asbestos exposure is proportional to cumulative exposure (duration X intensity) and underlying risk in the absence of exposure. Risk of death from mesothelioma appears proportional to cumulative exposure in a given period. Animal studies confirm the human epidemiological results. All major asbestos varieties produce lung cancer and mesothelioma, with only limited differences in carcinogenic potency. One can extrapolate the risks of asbestos cancers from occupational exposures, although the uncertainty is approximately tenfold or greater. Calculations of asbestos unit risk values are uncertain and based on subjective estimates because of the following limitations in data: (1) extrapolation from high occupational levels to much lower ambient levels; (2) the uncertainty of mass-to-fiber conversion; (3) statistical uncertainties; (4) various biases and confounding aspects of medical data; and very importantly, (5) nonrepresentative exposure estimates.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT Release to Public	**19. SECURITY CLASS** *(This Report)* Unclassified	**21. NO. OF PAGES** 215
	20. SECURITY CLASS *(This page)* Unclassified	**22. PRICE**

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

EPA/600/8-84/003F
June 1986

Airborne Asbestos
Health Assessment Update

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, N.C. 27711

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PREFACE

This Asbestos Health Assessment Update document has been prepared by the Environmental Criteria and Assessment Office of the U.S. Environmental Protection Agency (EPA), Office of Health and Environmental Assessment (OHEA). The document was developed to serve as the scientific basis for EPA review and revision, as appropriate, of the National Emission Standards for Asbestos as a hazardous air pollutant.

The document was reviewed and critiqued in July, 1984, by the Environmental Health Committee (EHC) of the U.S. EPA Science Advisory Board (SAB) and subsequently revised to take into account the peer-review comments of that SAB committee. The Science Advisory Board provides advice on scientific matters to the Administrator of the U.S. Environmental Protection Agency.

In the development of this assessment document, pertinent scientific literature has been critically evaluated and conclusions are presented in such a manner that the toxicity of asbestos and related characteristics are identified. Estimates of the fractional increased risk of lung cancer and mesothelioma per unit exposure of asbestos are also discussed, in an attempt to quantify adverse health effects associated with exposure to asbestos via inhalation.

ABSTRACT

Data developed since the early 1970s, from large population studies with long follow-up, have added to our knowledge of asbestos-related diseases and strengthened the evidence for associations between asbestos and specific types of health effects. Lung cancer and mesothelioma are the most important asbestos-related causes of death among exposed individuals. Cancer at other sites also has been associated with asbestos exposure. The accumulated data suggest that the excess risk of lung cancer from asbestos exposure is proportional to the cumulative exposure (the duration times the intensity) and the underlying risk in the absence of exposure. The risk of death from mesothelioma is approximately proportional to the cumulative exposure to asbestos and increases sharply with time since onset of exposure. Animal studies confirm the human epidemiological results and indicate that all major asbestos varieties produce lung cancer and mesothelioma, with only limited differences in carcinogenic potency. Some measurements demonstrate that asbestos exposures exceeding 100 times background occur in non-occupational environments. Currently, the most important of these non-occupational exposures is the release of fibers from asbestos-containing surfacing materials in schools, auditoriums, and other public buildings, or from sprayed asbestos fireproofing in high-rise office buildings. Extrapolations of risks of asbestos cancers from occupational circumstances can be made, although numerical estimates in a specific exposure circumstance have a large (approximately tenfold) uncertainty. Because of this uncertainty, calculations of unit risk values for asbestos at low concentrations must be viewed with caution. They are subjective, to some extent, and are also subject to the following limitations in data: 1) variability in the exposure-response relationship at high exposures; 2) uncertainty in extrapolating to exposures 1/100 as much; and 3) uncertainties in conversion of optical fiber counts to electron microscopic fiber counts or mass determinations.

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1. SUMMARY

Data developed since the early 1970s, from large population studies with long follow-up, have added to our knowledge of asbestos disease. These data strengthen and quantitatively define the association of asbestos exposure with disease. Lung cancer and mesothelioma are the most important asbestos-related causes of death among exposed individuals. Gastrointestinal cancers are also increased in most studies of occupationally exposed workers. Cancer at other sites (larynx, kidney, ovary) has also been shown to be associated with asbestos exposure in some studies, but the degree of excess risk and the strength of the association are less for these and the gastrointestinal cancers than for lung cancer or mesothelioma. The International Agency for Research on Cancer (1982) lists asbestos as a group 1 carcinogen, meaning that exposure to asbestos is carcinogenic to humans. EPA's proposed guidelines would categorize asbestos as Group A, human carcinogen (Federal Register, 1984b).

Data from a study of U.S. insulation workers allow models to be developed for the time and age dependence of lung cancer and mesothelioma risk. Thirteen other studies provide exposure-response information. The accumulated data suggest that the excess risk of death from lung cancer from asbestos exposure is proportional to the cumulative exposure (the duration times the intensity) and the underlying risk in the absence of exposure. The time course of lung cancer is determined primarily by the time course of the underlying risk. However, the risk of death from mesothelioma increases very rapidly after the onset of exposure and is independent of age and cigarette smoking. As with lung cancer, the risk appears to be proportional to the cumulative exposure to asbestos in a given period. The dose and time relationships for other asbestos cancers are uncertain.

Fourteen studies provide data for a best estimate fractional increased risk of lung cancer per unit exposure. The values characterizing the lung cancer risk obtained from different studies vary widely. Some of the variability can be attributed to specific processes. Chrysotile mining and milling, and perhaps friction product manufacture, appear to have lower unit exposure risks than chrysotile textile production and other uses of asbestos. Other variability can be associated with the uncertainties of small numbers in epidemiological studies and misestimates of the exposures of earlier years. Finally, some differences between studies may be related to differences in fiber type, but these are much less than those associated with specific processes.

Four studies provide similar quantitative data on the unit exposure risk for mesothelioma and six additional studies provide corroborative, but less accurate, quantitative data. The same factors that affect the lung cancer unit exposure risk appear to affect that of mesothelioma as the ratio of a measure of mesothelioma risk to excess lung cancer risk is roughly constant across the ten studies. However, in other studies the ratio of number of mesothelioma deaths to lung cancer deaths among groups exposed to substantial quantities of crocidolite is two to four times higher than among groups exposed predominantly to other fibers. Further, the risk of peritoneal mesothelioma appears to be less from exposure to chrysotile than to either crocidolite or amosite, but this suggestion is tempered by uncertainties associated with the greater possibility of misdiagnosis of the disease.

Animal studies confirm the human epidemiological results. All major asbestos varieties produce lung cancer and mesothelioma with only limited differences in carcinogenic potency. Implantation and injection studies show that fiber dimensionality, not chemistry, is the most important factor in fiber-induced carcinogenicity. Long (>4 μm) and thin (<1 μm) fibers are the most carcinogenic at a cancer-inducible site. However, the size dependence of the deposition and migration of fibers also affects their carcinogenic action in humans.

Measurements demonstrate that asbestos exposures exceeding 100 times the background occur to individuals in some non-occupational settings. Currently, the most important of these non-occupational exposures is from the release of fibers from asbestos-containing surfacing materials in schools, auditoriums, and other public buildings, or from sprayed asbestos-containing fireproofing in high-rise office buildings. A high potential exists for future exposure from the maintenance, repair, and removal of these materials.

Extrapolations of risks of asbestos cancers from occupational circumstances can be made, although numerical estimates in a specific exposure circumstance have a large (approximately tenfold) uncertainty. Because of this uncertainty, calculations of unit risk values for asbestos at the low concentrations measured in the environment must be viewed with caution. The best estimate of risk to the United States general population for a lifetime continuous exposure to 0.0001 f/ml is 2.8 mesothelioma deaths and 0.5 excess lung cancer deaths per 100,000 females. Corresponding numbers for males are

1.9 mesothelioma deaths and 1.7 excess lung cancer deaths per 100,000 individuals. Excess GI cancer mortality is approximately 10-30 percent that of excess lung cancer mortality. These risks are subjective, to some extent, and are also subject to the following limitations in data: 1) variability in the exposure-response relationship at high exposures; 2) uncertainty in extrapolating to exposures 1/100 as much; and 3) uncertainties in conversion of optical fiber counts to electron microscopic fiber counts or mass determinations.

Recently several government agencies in different countries reviewed asbestos health effects. Areas of agreement and disagreement between these other reviews and those of this document are presented. A comparison of the different risk estimates is provided.

2. INTRODUCTION

The principal objective of this "Airborne Asbestos Health Assessment Update" document is to provide the U.S. Environmental Protection Agency (EPA) with a sound scientific basis for review and revision, as appropriate, of the national emission standard for asbestos, 40 CFR 61, subpart B, as required by the 1977 Clean Air Act Amendments, Sections 111 and 112. The health effects basis for designating asbestos as a hazardous pollutant and minimizing emissions via the original 1973 National Emissions Standard for Hazardous Air Pollutants (NESHAP) was scrutinized, at that time, during two public hearings and a public comment period. Once a pollutant has been designated as a "hazardous" air pollutant, the burden of proof is placed on proving that designation wrong. The original health effects basis for designating asbestos as a hazardous air pollutant was qualitative evidence establishing asbestos-associated carcinogenic effects. However, insufficient bases then existed by which to define pertinent quantitative dose-response relationships; i.e., unit risk values could not be credibly estimated. The main focus of this update document is to describe asbestos-related health effects developments since 1972, and to determine if new data warrant the specification of unit risk values for asbestos. This report forms part of the basis to perform a risk assessment. The National Academy of Sciences (NAS) in 1983 suggested a definition of risk assessment as the use of the factual data base to define the health effects of exposure of individuals or populations to hazardous materials, such as asbestos in this case (National Academy of Sciences, 1983). This update document is not meant to characterize the status of asbestos measurement techniques or mineralogical characterization, although they are presented briefly as background information. Because this document is concerned only with the excess risk of cancer from inhalation of asbestos fibers, consideration of the risk posed from ingesting asbestos fibers also is outside its scope. A separate criteria document for asbestos in water is being prepared by the EPA.

Thus, emphasis is placed on the literature published after 1972 and on those papers that provide information on the risk from low-level exposures, such as those encountered in the non-occupational environment. Specifically, this report addresses the following issues:

1. Are there models that illustrate the age, time, and exposure dependence of asbestos diseases that can be used satisfactorily in a quantitative risk assessment?

2. Is there consistency among studies and sufficiently good estimates of exposure in occupational circumstances so that useful exposure-response relationships can be established?

3. Do these studies indicate any significant differences in the carcinogenic potency of different asbestos minerals or of fibers of different dimensionality?

4. What additional or confirmatory information relating to human carcinogenicity is provided by animal studies?

5. What are the non-occupational concentrations of asbestos to which populations are exposed?

6. Is there a basis for making numerical estimates of risks of asbestos disease that might result from non-occupational exposures?

Two documents provide good reviews of the status of knowledge of the health effects of asbestos in the early 1970s. One is the criteria document for occupational exposure to asbestos produced by the National Institute of Occupational Safety and Health as part of the Occupational Safety and Health Administration's consideration of an asbestos standard in early 1972 (National Institute for Occupational Safety and Health, 1972). The second is the proceedings of a conference sponsored by the International Agency for Research on Cancer (IARC), which was convened in October 1972 with the stated purpose of reviewing the knowledge of the biological effects of asbestos (Bogovski et al., 1973), and included a report by an Advisory Committee on Asbestos Cancers appointed by the IARC to review evidence relating exposures to asbestos dust to cancers.

2.1 SUMMARY OF ASBESTOS HEALTH EFFECTS THROUGH 1972

This section relies heavily on review articles found in the proceedings of the October 1972 IARC meeting and in the report of the IARC Advisory Committee published therein (Bogovski et al., 1973) for a summary of health effects knowledge as of 1973.

2.1.1 Occupational Exposure

Diseases considered to be associated with asbestos exposure in 1972 included asbestosis, mesothelioma, bronchogenic carcinoma, and cancers of the gastrointestinal (GI) tract, including the esophagus, stomach, colon, and rectum. Lung cancer was associated with exposure to all principal commercial varieties of asbestos fiber: amosite, anthophyllite, crocidolite, and chrysotile. Excess risks of bronchogenic carcinoma were documented in mining and milling, manufacturing, and end product use (application of insulation materials). Mesothelioma was a cause of death among factory employees, insulation applicators, and workmen employed in the mining and milling of crocidolite. A much lower risk of death from mesothelioma was observed among chrysotile or amosite mine and mill employees, and no cases were associated with anthophyllite exposure. The IARC Advisory Committee suggested that the risk of death from mesothelioma was greatest with crocidolite, less with amosite, and still less with chrysotile. This suggestion was based on the association of disease with exposures. No unit exposure risk information existed.

Information on exposure-response relationships for lung cancer risk among various exposed groups was scanty. Data from Canadian mine and mill employees clearly indicated an increasing risk with increasing exposure, measured in terms of millions of particles per cubic foot-years (mppcf-y), but data on the risk at minimal exposure were uncertain because the number of expected deaths calculated using adjacent county rates suggested that all exposure categories were at elevated risk (McDonald et al., 1971). A study of retirees of the largest U.S. asbestos manufacturer showed lung cancer risks ranging from 1.7 times that expected in the lowest exposure category to 5.6 times that expected in the highest (Enterline and Henderson, 1973). Exposures were expressed in mppcf-y and information on conversion of mppcf to fibers per milliliter was available only for textile production. Despite the paucity of data, the report of the Advisory Committee on Asbestos Cancers to the IARC (Bogovski et al., 1973) stated, "The evidence ... suggests that an excess lung carcinoma risk is not detectable when the occupational exposure has been low. These low occupational exposures have almost certainly been much greater than that to the public from general air pollution." Limited data existed on the association of GI cancer with asbestos exposure, but the "excess is relatively small compared with that for bronchial cancer."

The prevalence of asbestosis, particularly as manifested by X-ray abnormalities of the pleura or parenchymal tissue, had been documented more extensively than the risk of the asbestos-related malignancies. In part, this documentation resulted from knowledge of this disease extending back to the turn of the century, whereas the malignant potential of asbestos was not suggested until 1935 (Lynch and Smith, 1935; Gloyne, 1936) and not widely appreciated until the 1940s (Merewether, 1949). Asbestosis had been documented in a wide variety of work circumstances and associated with all commercial types of asbestos fibers. Among some heavily exposed groups, 50 to 80 percent of individuals employed for 20 or more years were found to have abnormal X-rays characteristic of asbestos exposure (Selikoff et al., 1965; Lewinsohn, 1972). A lower percentage of abnormal X-rays was present in lesser exposed groups. Company data supplied to the British Occupational Hygiene Society (British Occupational Hygiene Society, 1968) on X-ray and clinical abnormalities among 290 employees of a large textile production facility in Great Britain were analyzed by Berry (1973) in terms of a fiber exposure-response relationship. The results were utilized in establishing the 1969 British regulation on asbestos. These data, shown in Figure 2-1, suggested that the risk of developing the earliest signs of asbestosis (rales) was less than 1 percent for accumulated fiber exposure of 100 fiber-years/ml (f-y/ml), e.g., 2 fibers/milliliter (f/ml) for 50 years. However, shortly after the establishment of the British Standard, additional data from the same factory population suggested a much greater prevalance of X-ray abnormalities than was believed to exist at the time the British Standard was set (Lewinsohn, 1972). These data resulted from use of the new International Labour Office (ILO) U/C standard classification of X-rays (International Labour Office, 1971) and the longer time from onset of employment. Of the 290 employees whose clinical data were reviewed by the BOHS, only 13 had been employed for 30 or more years; 172 had less than 20 years of employment. The progression of asbestosis depends on both cumulative exposure and time from exposure; therefore, analysis in terms of only one variable (as in Figure 2-1) can be misleading.

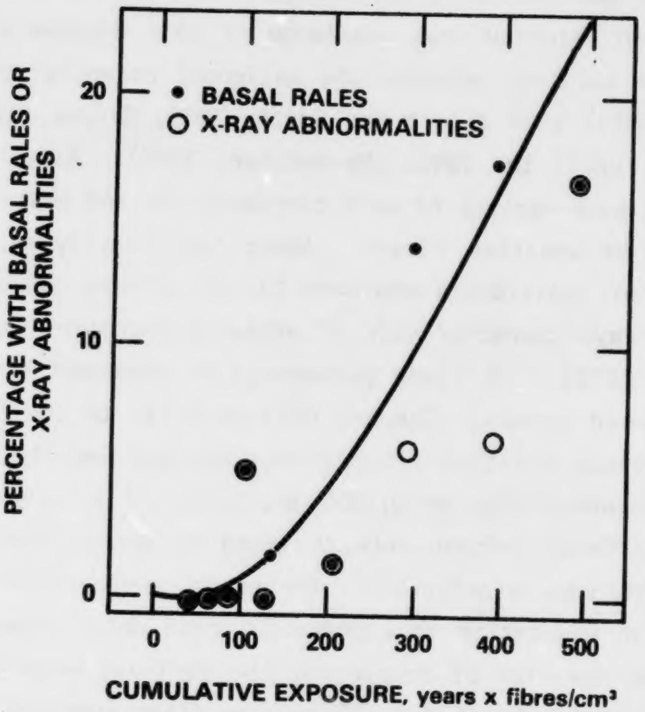

Figure 2-1. Dose-response relationship for prevalence of basal rales in a chrysotile asbestos factory.

Source: Berry (1973); x-ray data added from British Occupational Hygiene Society (1968).

2.1.2 Environmental and Indirect Occupational Exposure Circumstances

Several research groups had shown that asbestos disease risk could develop from other than direct occupational exposures. Wagner, Sleggs, and Marchand (1960) showed that a mesothelioma risk in environmental circumstances existed in the mining areas of the Northwest Cape Province of South Africa. Of 33 mesotheliomas reported over a 5-year period, roughly half were from occupational exposure. However, all but one of the remainder resulted from exposure occasioned by living or working in the area of the mining activity. A second study that showed an extra-occupational risk was that of Newhouse and Thompson (1965) who investigated the occupational and residential background of 76 individuals deceased of mesothelioma in the London hospital. Forty-five of the decedents had been employed in an asbestos industry; of the remaining 31, 9 lived with someone employed in asbestos work and 11 were individuals who resided within half a mile of an asbestos factory. Bohlig and Hain (1973) identified environmental asbestos exposure in 38 mesothelioma cases without occupational exposure who resided near an asbestos factory, further defining residential risk. A final study, which is particularly important because of the size of the population implied to be at risk, was that of Harries (1968), who pointed to a risk of asbestos disease from indirect occupational exposure in the shipbuilding industry. He described the presence of asbestosis in 13 individuals and mesothelioma in 5 others who were employed in a shipyard, but were not members of trades that regularly used asbestos. Rather, they were exposed to the dust created by other employees placing or removing insulation.

Evidence of ubiquitous general population exposure and environmental contamination from the spraying of asbestos on the steel-work of high rise buildings was established by 1972. Data by Nicholson and Pundsack (1973) showed that asbestos was commonly found at concentrations of nanograms per cubic meter (ng/m^3) in virtually all United States cities, and at concentrations of micrograms per liter (μg/l) in river systems of the United States. Concentrations of hundreds of nanograms per cubic meter were documented at distances up to one-quarter of a mile from fireproofing sites. Mesothelioma was acknowledged by the Advisory Committee to be associated with environmental exposures, but they suggested that "the evidence relates to conditions many years ago .... There is no evidence of a risk to the general public at present." Further, their report stated that, "There is at present no evidence of lung damage by asbestos to the general public," and "Such evidence as there is does not indicate any risk" from asbestos fibers in water, beverages, food, or parenteral drugs. No mention was made in the report of risks from indirect occupational asbestos exposures.

2.1.3 Analytical Methodology

During the late 1960s and early 1970s, significantly improved methods were developed for assessing asbestos disease and quantifying asbestos in the environment. In 1971, a standardized methodology was established for the identification of pneumoconiosis: the ILO U/C Classification of Pneumoconioses (International Labour Office, 1971). This methodology provided a uniform criterion for assessing the prevalence of asbestos-related X-ray abnormalities.

Significant advances were also achieved in the quantification of asbestos aerosols. In the late 1960s, the membrane filter technique was developed for the measurement of asbestos fibers in workplace aerosols. While this procedure has some limitations, it did establish a standardized method, using simple instrumentation, that was far superior to any that existed previously. This method subsequently allowed epidemiological studies to be done that based exposure estimates on a standardized criterion. Experimental techniques in the quantification of asbestos at concentrations of tenths of ng/m^3 of air and tenths of µg/l of water were also developed, extending the sensitivity of exposure estimates approximately three orders of magnitude below those of occupational aerosols and allowing assessment of general population exposures. Finally, techniques for the analysis of asbestos in lung and other body tissues were developed. Digestion techniques and the use of electron microscopy to analyze fibers contained in the digest and in thin sections of lung tissue showed that asbestos fibers were commonly present in the lung tissue of general population residents as well as individuals exposed in occupational circumstances.

2.1.4 Experimental Studies

Experimental animal studies using asbestos fibers confirmed the risks of lung cancer and mesothelioma from amosite, crocidolite, and chrysotile. In each case, the establishment of a risk in animals followed the association of the malignancy with human exposure. For example, a causal relationship between lung cancer and asbestos exposure in humans was suggested in 1935 and confirmed in the late 1940's, but was not described in the open literature in animals until 1967 (Gross et al., 1967). Mesothelioma, reported in an asbestos worker in 1953 (Weiss, 1953), was produced in animal experimentation in 1965 (Smith et al., 1965). Other animal experimentation showed that combinations of asbestos and other carcinogenic materials produced an enhanced risk of asbestos cancer. Asbestos exposure combined with exposure to benz(a)pyrene was demonstrably more carcinogenic than exposure to either agent alone. Additionally, organic and metal compounds associated with asbestos fibers were ruled out as important factors in the carcinogenicity of fibers. Lastly, animal experimentation involving the application of fibers onto the pleura of animals indicated that the important factor in the carcinogenicity was the length and width of the fibers rather than their chemical properties (Stanton, 1973). The greatest carcinogenicity was related to fibers that were less than 2.5 μm in diameter and longer than 10 μm.

2.2 CURRENT ASBESTOS STANDARDS

The current Occupational Safety and Health Administration (OSHA) standards for an 8-hour time-weighted average (TWA) occupational exposure to asbestos is 2 fibers longer than 5 μm in length per milliliter of air (2 f/ml or 2,000,000 f/m^3). Peak exposures of up to 10 f/ml are permitted for no more than 10 min (Code of Federal Regulations, 1984a). This standard has been in effect since July 1, 1976, when it replaced an earlier one of 5 f/ml (TWA). In Great Britain, a value of 0.5 f/ml is now the accepted level for chrysotile. This standard has evolved from recommendations made in 1979 by the Advisory Committee on Asbestos (1979a), which also recommended a TWA of 0.5 f/ml for amosite and 0.2 f/ml for crocidolite. From 1969 to 1983, 2 f/ml (TWA) was the standard for chrysotile (British Occupational Hygiene Society, 1968). This earlier British standard served as a guide for the OSHA standard (National Institute for Occupational Safety and Health, 1972).

The 1969 British standard was developed specifically to prevent asbestosis among working populations; data that would allow a determination of a standard for cancer (British Occupational Hygiene Society, 1968) were felt to be lacking. Unfortunately, among occupational groups, cancer is the primary cause of excess death among workers (see Chapter 3). Three-fourths or more of asbestos-related deaths are from malignancy. This fact led OSHA to propose a lowered TWA standard to 0.5 f/ml (500,000 f/m^3) in October, 1975 (Federal Register, 1975). The National Institute for Occupational Safety and Health anticipated hearings on a new standard and proposed a value of 0.1 f/ml (National Institute for Occupational Safety and Health, 1976) in an update of their 1972 criteria document. In the discussion of the NIOSH proposal, it was stated that the value was selected on the basis of the practical limitations of analytical techniques using optical microscopy, and that 0.1 f/ml may not necessarily protect against cancer. The preamble to the OSHA proposal acknowledges that no information exists by which to define a threshold for asbestos carcinogenesis. The OSHA proposal has been withdrawn, and a new proposal was submitted on April 10, 1984 (Federal Register, 1984a). In it, OSHA proposed a TWA standard of either 0.2 or 0.5 f/ml, depending upon information to be obtained in hearings (held during the summer of 1984). NIOSH reaffirmed its position on a 0.1 f/ml TWA standard (Occupational Safety and Health Administration, 1984).

The existing Federal national emission standards for asbestos are published in Part 61, Title 40, Code of Federal Regulations (1984b). In summary, these apply to milling, manufacturing, and fabrication sources, and to demolition, renovation, and waste disposal, and include other limitations. In general, the standards allow compliance alternatives, either (1) no visible emissions, or (2) employment of specified control techniques. The standards do not include any mass or fiber count emission limitations. However, some local governmental agencies have numerical standards (e.g., New York: 27 ng/m^3), but these have little regulatory relevance.

3. HUMAN HEALTH EFFECTS ASSOCIATED WITH OCCUPATIONAL EXPOSURE TO ASBESTOS

3.1 INTRODUCTION

The evidence that asbestos is a human carcinogen is overwhelming. Studies on more than 30 cohorts of workers exposed to asbestos have demonstrated an elevated risk of cancer at the 5% level of significance. All four major commercial varieties have been linked to excess cancer and asbestosis. The question is not so much what disease, but how much disease. Our concerns are now more quantitative than qualitative. What are the dose, time, and age relationships for the different asbestos cancers? Are there differences in the carcinogenic potencies of the different asbestos minerals? What are the cancer risks at low exposures? What are the estimates of uncertainty?

This chapter is largely concerned with those studies that provide quantitative exposure-response relationships for asbestos diseases. While lung cancer and mesothelioma are the most dominant asbestos-related malignancies, the strength of the evidence and the relative excess of cancers at other sites are discussed. Models for assessment of the risk of lung cancer and mesothelioma are reviewed. Unit exposure risks are estimated from 14 studies that provide information on exposure-response relationships. These estimates illustrate considerable variation in the calculated unit exposure risks for mesothelioma and lung cancer in the different studies. The magnitude and possible sources of these different unit risks are discussed. The extent to which the variation is the result of methodological or statistical uncertainties (i.e., on the estimates of exposure or of the magnitude of disease) or of differences in the character of the exposure in terms of fiber size and mineralogical species is considered in detail.

3.2 MORTALITY ASSOCIATED WITH ASBESTOS EXPOSURE

The study of U.S. and Canadian insulation workers by Selikoff et al. (1979) contains the largest number of asbestos-related deaths among any group of asbestos workers studied. Thus, it best demonstrates the full spectrum of disease from asbestos exposure. The mortality experience of 17,800 asbestos insulation workers was studied prospectively from January 1, 1967 through

December 31, 1976. These workers were exposed primarily to chrysotile prior to 1940, to chrysotile and amosite from 1940 through 1965, and largely to chrysotile thereafter. No crocidolite is known to have been used in the U. S. insulation material (Selikoff et al. 1970). The workers mainly applied new insulation; removal of old materials would have constituted less than 5% of their activities.

In this group, 2271 deaths occurred, and their analysis provides important insights into the nature of asbestos disease. Table 3-1 lists the expected and observed deaths by cause, and includes data on tumors less frequently found. Lung tumors were common and accounted for approximately 21 percent of the deaths; 8 percent were from mesothelioma of the pleura or peritoneum, and 7 percent died from asbestosis. Considering all cancers, 675 excess malignancies occurred, constituting 30 percent of all deaths. In addition to lung cancer and mesothelioma, the incidences of cancers of the gastrointestinal tract, larynx, pharynx and buccal cavity, and kidney were significantly elevated.

Other tumors were also increased, but not to a statistically significant degree for individual sites. However, these other cancers, as a group, were significantly in excess: 184 observed (using best available evidence for classification) versus 131.8 expected ($p<0.001$). Some of this excess, however, may be the result of misclassification of asbestos-related lung cancer or peritoneal mesothelioma. Rather than 184 deaths, certificate of death classification attributed 252 cancers to these other sites. After a review of pathological material and available medical records, pancreatic, liver, and unspecified abdominal cancers are found to be commonly misclassified. Individuals certified as dying of cancers of the pancreas and the abdomen were often found to have peritoneal mesotheliomas, and several liver cancers were the result of a primary malignancy in the lung. As it was not possible to review all cases, some additional misclassification may still exist. However, its magnitude would not be great compared to the remaining excess of 52 cases. The excess at extra-thoracic sites may reflect mortality from the dissemination of asbestos fibers to various organs (Langer, 1974). Alternatively, it has been suggested that asbestos could exert a systemic effect, perhaps on the immune system, that leads to a general increased risk of cancer (Goldsmith, 1982).

TABLE 3-1. DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA, JANUARY 1, 1967 - DECEMBER 31, 1976, NUMBER OF MEN 17,800, MAN-YEARS OF OBSERVATION 166,853

	Number of Deaths				
Underlying cause of death	Expected[a]	Observed		Ratio of observed to expected	
		BE	DC	BE	DC
Total deaths, all causes	1658.9	2271	2271	1.37	1.37
Total cancer, all sites	319.7	995	922	3.11	2.88
Cancer of lung	105.6	486	429	4.60	4.06
Pleural mesothelioma	-[b]	63	25	-[b]	-[b]
Peritoneal mesothelioma	-[b]	112	24	-[b]	-[b]
Mesothelioma, n.o.s.	-[b]	0	55	-[b]	-[b]
Cancer of esophagus	7.1	18	18	2.53	2.53
Cancer of stomach	14.2	22	18	1.54	1.26
Cancer of colon-rectum	38.1	59	58	1.55	1.52
Cancer of larynx	4.7	11	9	2.34	1.91
Cancer of pharynx, buccal cavity	10.1	21	16	2.08	1.59
Cancer of kidney	8.1	19	18	2.36	2.23
Cancer of pancreas	17.5	23	49	1.32	2.81
Cancer of liver and biliary passages	7.2	5	19	0.70	2.65
Cancer of brain	10.4	14	17	1.35	1.63
Cancer of lymphatic and hematopoietic system	33.2	34	31	1.02	0.93
All other cancer	63.5	108	136	1.65	2.16
Noninfectious pulmonary diseases, total	59.0	212	188	3.59	3.19
Asbestosis	-[b]	168	78	-[b]	-[b]
All other causes	1280.2	1064	1161	0.83	0.91

BE = Best evidence. Number of deaths categorized after review of best available information (autopsy, surgical, clinical)

DC = Number of deaths as recorded from death certificate information only.

[a] Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Statistics, 1967-1976. (National Center for Health Statistics, 1977).

[b] Rates and thus ratios are not available, but these have been rare causes of death in the general population.

Source: Selikoff et al. (1979).

3.2.1 Accuracy of Cause of Death Ascertainment

Table 3-1 lists the observed deaths according to the cause recorded on the certificate of death (DC) and according to the best evidence (BE) available from medical records, surgical specimens, and autopsy protocols. In comparing occupational mortality with that of the general population, one usually utilizes information as recorded on death certificates since such information, without verification, serves as the basis for "expected rates." However, since mesothelioma and asbestosis are virtually unseen in the general population, their misdiagnosis (which has been common) is of little importance. In contrast, their misdiagnosis among asbestos workers can cause serious distortions in cause-specific mortality. Not only are asbestos-related causes understated, but others, such as pancreatic cancer, might wrongly appear to be significantly elevated (Selikoff and Seidman, 1981). While substantial differences exist in the DC and BE characterization of deaths from mesothelioma, asbestosis, pancreatic cancer, and liver cancer, the numbers of BE and DC deaths from cancer of other specific sites agree reasonably well.

Mesothelioma is best described by an absolute risk model and lung cancer by a relative risk model. Thus, risks for mesothelioma are expressed in absolute rates (e.g., deaths/1000 person-years), and the best medical evidence is used, when available, to establish the number of cases. Deaths from asbestosis are treated similarly. Risks for lung cancer are quantified by the ratio of observed to expected deaths. Here, it is expected that misclassification of lung cancer deaths would occur as frequently in asbestos workers as in the general population (in terms of the percentage of lung cancer cases). Therefore, the certificate of death cause is used to establish the relative risks of lung cancer in asbestos-exposed groups. However, when possible, account is taken of deaths from mesothelioma and asbestosis. The treatment of other malignancies also uses DC causes of death.

3.3 EPIDEMIOLOGICAL STUDIES OF ASBESTOS HEALTH EFFECTS: STRENGTH OF THE EVIDENCE

Many epidemiological studies have documented the presence of asbestos disease among occupationally-exposed workers. The larger and more recent studies are listed in Table 3-2 according to the type of fiber exposure and

TABLE 3-2. OBSERVED AND EXPECTED DEATHS FROM ALL CAUSES, LUNG CANCER, GASTROINTESTINAL CANCER, AND MESOTHELIOMA IN 41 ASBESTOS-EXPOSED COHORTS

	Industry	Country	Sex	COHORT Total Number	COHORT % Untraced	Years of follow-up	Years from onset	ALL DEATHS Obs.	ALL DEATHS Exp.	ALL DEATHS SMR	LUNG CANCER[a] Obs.	LUNG CANCER[a] Exp.	LUNG CANCER[a] SMR	GI CANCER[a] Obs.	GI CANCER[a] Exp.	GI CANCER[a] SMR	Number of mesotheliomas Pl	Number of mesotheliomas Per	Unspec	Asbestosis	Other cancers in excess at 95% sign. level
Chrysotile																					
Acheson et al. (1982)	Gas mask	UK	F	570	0.9	1951-1980	10+	177	148.5	119	6	4.5	133	4	4.9	82	1	0			
Dement et al. (1983)[b]	Textiles	USA	M	1261	2.1	1940-75	15+	245	152.5	161	33	9.8	336*	10	8.1	124	0	1		17	
McDonald et al. (1983a,b)[b]	Textiles	USA	M	2543		1938-77	20+	570	447.	127	59	29.6	200*	26	17.1	152*	0	1		20	
McDonald et al. (1980)	Mining	Canada	M	9767	10.0	1926-75	20+	3291	3019.3	109	230	184.0	125*	209	203.7	103	10	0		46	
McDonald et al. (1980)	Mining	Canada	F	440	7.0	1926-75	20+	84			1	1.2	83				1	0		0	
Nicholson et al. (1979)[c]	Mining	Canada	M	544	8.0	1961-77	20+	178	159.9	111	25	11.1	225*	10	9.5	105	1			26	
McDonald et al. (1984)	Frict. prod.	USA	M	3177	3.5	1938-77	20+	803	740.1	109	73	49.1	149*	59	51.6	114	0[d]	0		0[e]	
Rubino et al. (1979)	Mining	Italy	M	952	2.0	1946-75	20+	220	160.2	137	9	8.7	103	15	14.5	103	1[f]	0		21.1	Larynx[g]
Weiss (1977)	Manufacturing	USA	M	254	6.1	1945-74		66	108.8	61	4	4.3	93	4	3.8	105	0	0			
Predominantly chrysotile (>98%)																					
McDonald et al. (1983b)[h]	Tex. frict.	USA	M	4137	2.7	1938-77	20+	895	821.1	109	53	50.5	105	54	47.9	113	10	4		59	
Robinson et al. (1979)[h]	Tex. frict.	USA	M	2722	2.1	1940-75	0	912	741.3	123	49	36.1	136*	50	41.4	121	4	5	4	59.5	
Robinson et al. (1979)[h]	Tex. frict.	USA	F	554	3.1	1940-75		128	88.3	145	14	1.7	824*	8	6.0	133	1	1	2	13.1	
Mancuso & El-attar (1967)[h]	Tex. frict.	USA	MF	1493		1940-64		330	139.7	236	33	14.8	223*	16	8.9	180*	1	0		31	
Peto (1977)[i]	Textiles	UK	M	822	3.2	1933-74	10+	293	224.9	130	49	22.9	214*	16	15.7	102	9	0		20.6	
Thomas et al. (1982)[j]	Cement prod.	UK	M	1592	3.3	1936-77	15+	261	243.2	107	22	25.8	85	14	14.1	99	2	0		0	
Amosite																					
Acheson et al. (1984)[k]	Manufacturing	UK	M	4820	0.5	1947-78		333	298.8	111	57	29.1	196*	19	17.1	111	4	1		8.9	
Seidman et al. (1979)	Manufacturing	USA	M	820	4.6	1961-76	5+	528	397.2	133	83	21.9	380*	28	22.7	123	7	7		30	
Predominantly crocidolite[l]																					
Acheson et al. (1982)	Gas mask	UK	F	757	2.4	1951-80	10+	219	203.5	107	13	6.6	197*	5	4.0	125	3	2			Ovary
Hobbs et al. (1980)	Mining	Austral.	M	6200	20.0	1938-78	15+	526	587.2	90	60	38.2	157*				17	0		14	
Jones et al. (1980)[m]	Gas mask	UK	F	951	39.2	1941-78		166			12	6.3	190*	10	20.3	49	13	4			
Wignall & Fox (1982)[m]	Gas mask	UK	F	523	6.5	1951-77	10+	133	139.0	96	10	3.7	273*	7	10.7	65	9	3		1	Ovary
McDonald & McDonald (1978)	Gas mask	Canada	MF	199	11.6	1939-75		53			7	2.4[n]	875*				3	6		4	
Anthophyllite																					
Nurminen et al. (1974)	Mining	Finland	MF	1092	4.7	1936-69		248			21	12.6	167*	7	14.9	47	0	0		13	
Talc (Tremolite)																					
Kleinfeld et al. (1974)	Mining	USA	M	260		1944-69	15+	108			13	4.5	289*	7	6.9	101	0	1		29	
Brown et al. (1979)	Mining	USA	M	398	4.0	1947-75		74	61.3	120	9	3.3	270*	3	3.0	100	0	0	1[o]	3.7	
Mixed Exposures																					
Albin et al. (1984)	Cement prod.	Sweden	M	598	3.8	1957-80	10+	172	157.4	109	12	6.6	183*	19	10.8	176*	4	0		10.1	
Berry & Newhouse (1983)	Frict. prod.	UK	M	7474		1942-80	10+	1339	1361.8	98	143	139.5	103	103	107.2	96	8	0			
Berry & Newhouse (1983)	Frict. prod.	UK	F	3708		1942-80	10+	299	328.0	91	6	11.3	53	29	27.4	106	2	0			
Elmes & Simpson (1977)	Insulation	UK	M	170	2.9	1940-75		122	55.5	220	27	5	540*	13	1	1300*	8	5	11[p]	19	
Finkelstein (1983)	Cement prod.	Canada	M	241	3.3	1963-80	15+	72	42.5	169	20	3.3	606*	4	2.5	160	6	5		5.5	
Henderson & Enterline (1979)	Manufacturing	USA	M	1075		1941-73	Ret.	781	648.7	120	63	23.3	270*	55	39.9	138*	5	0		50	
Selikoff et al. (1979)	Insulation	USA	M	17800		1967-76	20+	1946	1376.0	141	390	93.7	416*	89	53.2	167*	63	112		160	Kidney
Selikoff et al. (1979)	Insulation	USA	M	632		1943-76	20+	469	319.9	147	93[q]	13.1[n]	710*	43[q]	14.8	~291*	11	27		41	
Kleinfeld et al. (1967)	Insulation	USA	M	152		1945-65	15+	46			10	1.4[n]	702*	5	1.8	278*	1	2		2	
Kolonel et al. (1980)	Shipyard	USA	M	4779	8.0	1950-70	20+	112	116.9	96	13	7.5	173				0[r]	0			
Newhouse & Berry (1979)	Manufacturing	UK	M	4600		1936-75	10+	545	438.0	124	103	43.2	238*	40	34	118	19	27		16.3	
Newhouse & Berry (1979)	Manufacturing	UK	F	922	23.	1936-75	10+	200	118.0	169	27	3.2	843*	20	10.2	196*	13	8		6.7	
Nicholson (1976a)	Manufacturing	USA	MF	689	0.0	1959-71	20+	199	134.3	148	27	8.4	321*	13	5.0	260*	8	7		24	
Puntoni et al. (1979)	Shipyard	Italy	M	42647		1960-75		1070	853.7	125	123	54.9	224*	66	48.6	136				50.6	Kidney, urinary organs, and larynx
Rossiter & Coles (1980)	Shipyard	UK	M	6292	3.4	1947-78		1043	998.4	104	84	100.3	84	63	76.2	83			31	9	
Weill (1984)	Cement prod.	USA	M	5645	25.	1940-74	20+	601	890.1	68	51	49.2	104	25	50.1	50	0[s]	0			

Footnotes for Table 3-2

a. The deaths from lung cancer and gastrointestinal cancer are those designated on the certificate of death. The cases of mesothelioma are those determined from the review of all available evidence. Such cases will not be included with the lung cancers. The asbestosis cases will be those specifically listed, when provided. Otherwise, the number will be the difference between the observed and expected for non-infectious respiratory disease. The latter can be identified by the use of the decimal point notation.

b. Two studies of the same plant but with different cohort definitions.

c. The majority of this cohort would also be included in that of McDonald et al. (1980).

d. No mesotheliomas were identified in the defined cohort. However, three mesotheliomas, two in women and one in an individual terminated prior to 1937, from this plant have been identified in the Tumor Registry of Connecticut (Teta et al., 1983).

e. Twelve cases of pneumoconiosis were identified in this cohort. However, these were all in individuals who had previous exposure to anthracite coal containing silica.

f. Death certificate diagnosis of mesothelioma based upon clinical findings and analysis of pleural fluid. No histological material was available for review.

g. Significant at the 5 percent level in the entire cohort.

h. Three studies of the same plant at different periods of time and with different cohort definitions. Between 3000 and 6000 tons of chrysotile were used annually. Amosite constituted less than 1 percent of the asbestos used except for a 3-year period, 1942-1944, where an average of 375 tons per year were used. Crocidolite usage was approximately 3-5 tons per year (Robinson et al., 1979).

i. Between 1931 and 1970 an average of 60 tons of crocidolite per year were used (Berry et al., 1979). This would probably constitute about 1 percent of the total fiber usage.

j. The factory operated between 1932 and 1980. Between 1932 and 1935 crocidolite and chrysotile asbestos were used; thereafter, only chrysotile. The two mesotheliomas in this study were in the group exposed to both chrysotile and crocidolite.

k. Amosite was the predominant fiber used. However, chrysotile was also used between 1946 and 1973.

l. All of the groups in this category had a high exposure to crocidolite. In some cases, however, there was also a substantial exposure to chrysotile as well.

m. Two cohorts at the same facility with different definitions and follow-up periods.

n. Estimated as a proportion of deaths.

o. May have had exposure to asbestos in the construction industry.

p. Pleural mesothelioma or lung cancer.

q. Number of deaths based upon a review of all medical evidence.

r. No cases observed through the period of follow-up. Three cases have occurred subsequently.

s. No cases occurred in the cohort as defined during the period of observation. Two occurred in individuals prior to 20 years from onset of employment and nine cases (8 pleural and 1 peritoneal) have developed subsequent to termination of follow-up (Weill, 1984).

*$p < 0.05$.

work circumstance. Of the 41 groups listed, significantly increased (at the 5% level with a one-sided test) lung cancer is found in 32. Gastrointestinal cancers are elevated at a significant level in 10. Moreover, strong exposure-response relationships are seen for lung cancer and mesothelioma. They are also seen for gastrointestinal cancer, but to a lesser extent.

The follow-up period was relatively long in most of the studies listed in Table 3-2. However, in many cohorts, individuals continued to enter the studies through the follow-up years, particularly in the period after World War II. Thus, many individuals in some groups are just now reaching a time of high potential risk for mesothelioma (30 or more years from onset of exposure). In some cases, this can be seen in the finding of substantially increased risks of mesothelioma subsequent to the termination of follow-up (see Table 3-2 footnotes).

3.4 MATHEMATICAL MODELS OF HUMAN CARCINOGENESIS

The quantitative determination of cancer risk in an occupational group can be used to predict risks in similar exposure circumstances in the absence of any model of action; observations in one group would apply to identically exposed workers. If, however, a risk determination fits within the framework of a general mathematical model for cancer, then predictions outside the range of measurement can be made within the range of validity of a model. Validation of a mathematical model, of course, requires the testing of such predictions. If a mathematical model has a mechanistic basis, e.g., at a molecular level of action, its use is considerably strengthened. To the extent that a model is applicable, it strengthens risk estimates made for exposures and times different from those directly observed. To the extent that a model may be applicable, it points to issues that must be considered in any general risk assessment.

In the case of human carcinogenesis, a variety of multistage models have been proposed to describe a number of observations, most notably the power law dependence of human cancer risk with age and the time and dose dependence of induced malignancy in some animal experiments. The models were initially suggested to explain the observation that site-specific cancer mortality increases as the fifth or sixth power of age (e.g., Cook et al., 1969; Armitage and Doll, 1954). The models suggested ranged from proposals that multiple (up to six or seven) mutations (or carcinogenic events) occur in the same or adjacent cells (Muller, 1951; Fisher and Holloman, 1951; Nordling, 1953) to models that involve preferential clonal development of altered cell lines (Fisher, 1958; Armitage and Doll, 1957, 1961). Depending on the model, some or all of the states are capable of being affected by an external carcinogen. For those susceptible states, it is expected that the probability of progression to the next stage would be proportional to the time that a carcinogenic agent, or its active metabolite, is at a reaction site. A constant exposure to environmental carcinogens would then introduce a power of time for each state that is affected by a particular external carcinogen. Powers of time also arise from exposure-independent processes. It is important to note, however, that a power of dose is introduced for each exposure-dependent step (for short-term exposures). Motivated by the experimental demonstration of initiation and promotion in skin cancer (Berenblum and Shubik, 1949), Armitage and Doll (1957) discuss a two-state model with an intermediate time-dependent growth phase that is compatible with the observed age dependence of cancer incidence.

In its generalized form, the model suggests that the time dependence of site-specific cancer incidence in the general population is

$$I(t) = C\lambda_1\lambda_2 \ldots \lambda_k(t-w)^{k-1} \qquad (3\text{-}1)$$

where the λ_i are the transition probabilities of each state, k is the number of stages and w is the growth time for a fully transformed cell to become clinically detectable. One, or several, of the λ_i can be influenced by the application of an external carcinogen. There would be a power of dose (or intensity of exposure) for each stage so affected. To account for this, the most general form of the multistage model can be written

$$I(t) = C(q_0 + \Sigma_i q_i d^i)(t-w)^{k-1} \qquad (3\text{-}2)$$

Within this model, one can consider carcinogenic action on specific stages at different times in the carcinogenic process.

Whittemore (1977a, 1977b) and Day and Brown (1980) have explored some of the time courses of cancer risk that are predicted by the model. The important aspects of these analyses are:

1. The effects of early stage carcinogens are most important early in life (the cells or cell lines that are started in the carcinogenic process are available for a long time for further alteration). In addition, their effect diminishes slowly after cessation of exposures relative to continuous exposure.

2. The effects of late-stage carcinogens are most important late in life when many altered cells are available to be acted upon. The effects of exposure to late-stage carcinogens diminish rapidly after cessation of exposure.

3. For each stage that an externally applied carcinogen acts, there is a power of intensity of exposure (or dose for short-term exposures).

Thus, the predicted time dependence of cancer risk can be highly varied depending on the stage affected, and sublinear, as well as linear, dose-response relationships can be incorporated within the model. Here, sublinear refers to a relationship that contains a power of dose greater than unity. A supralinear relationship is not contained within the framework of the model.

The multistage model has provided a basis for dose-incidence extrapolation procedures. These have been formulated by Guess, Crump, and others (Guess and Crump, 1976, 1978; Guess et al., 1977). The procedure makes no a priori assumptions on the dose-response relationship, but utilizes a maximum likelihood procedure to calculate the q_i values along with their 95 percent confidence limits. In practice, it is found that most experimental carcinogenesis data cannot rule out a linear dose term. Thus, the 95 percent confidence limit on the risk at low exposure is dominated by the uncertainty on the linear term (Guess et al., 1977).

It should be noted that the exposure in the multistage model is to the site of action of an alterable cell. Significant non-linearities can be introduced into an exposure-response relationship by non-linearities in the metabolism of a chemical to an active species or in the detoxification of an active chemical. Such non-linearities have been observed in the case of vinyl chloride (Gehring et al., 1978). A general discussion of activation non-linearities in dose-response relationships has been published by Hoel et al. (1983).

Human data supporting a multistage model are limited because of lack of information on the age, time, and dose dependence of cancer risk from exposure to external agents. Recent data from the study of smoking effects among British doctors (Doll and Peto, 1978) suggest that the dose-response relationship is quadratic and that cigarette smoke may act at two stages, one early and one late, in the carcinogenic process. This concept is supported by the partial reduction in lung cancer risk after smoking cessation (relative to continued smoking). On the other hand, U.S. smoking data suggest a linear dose-response relationship (Hammond, 1966; Kahn, 1966). In the case of radiation, the long lasting increased risk of solid tumors among residents of Hiroshima and Nagasaki (Beebe et al., 1978) suggests an early stage action for radiation. However, the age dependence of risk demonstrates a risk that is proportional to the risk in the absence of radiation exposure, suggesting a late-stage action. The dose-response relationship, however, does not suggest a supra-linear relationship, which would be the case if two stages were affected. In contrast to a somewhat equivocal application to human data, the model describes very well the time and dose dependence of skin tumors in benzo(a)pyrene painted mice (Lee and O'Neill, 1971; Peto et al., 1975).

In summary, the multistage model provides a useful conceptual framework for considering the age, time and dose dependence of site specific cancer incidence. However, it is so general that it can be made to fit virtually any animal or human carcinogenesis dose-response data. The requirements are more stringent for fitting time-to-tumor data. Here, however, few human data are available for validation. At this time, the model cannot predict a priori either the dose or time dependence of human cancer. Nevertheless, the concepts of the model are plausible and warrant consideration when the data on the age, time, and dose dependence of asbestos cancers are reviewed.

3.5 LINEARITY OF EXPOSURE-RESPONSE RELATIONSHIPS

Direct evidence for linearity of response with asbestos exposure is available from seven studies (two of the same plant) that compared lung cancer mortality to the cumulative total dust exposure in asbestos workplaces (Dement et al.,.1982; Henderson and Enterline, 1979; McDonald et al., 1980, 1983a, 1983b; Finkelstein, 1983; Seidman, 1984). Figure 3-1 plots the exposure-response data in these studies as the ratio of observed to expected lung

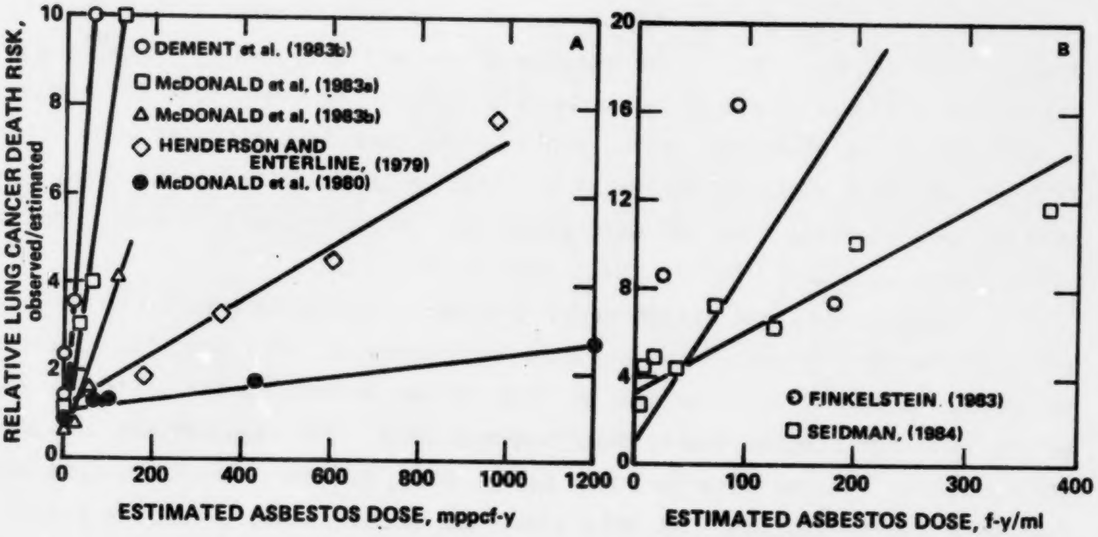

Figure 3-1. Exposure response relationships for lung cancer observed in seven studies. Cumulative exposures are measured in terms of millions of particles per cubic foot-years (mppcf-y) or fibers per milliliter-years (f-y/ml).

cancer mortality against the measured cumulative dust exposure in millions of particles per cubic foot-years (mppcf-y) or cumulative asbestos exposure in fiber-years per milliliter (f-y/ml). (Henceforth, the term "dose" will be used to designate cumulative exposure.) While different exposure-response relationships appear to exist for the five studies of Figure 3-1a, each demonstrates a very good linear relationship over the entire range of observation. The differences in the slopes of the relationships may relate to differences in the quantity of the other dust present, the fiber size distribution, the fiber type, the age of the population under observation, the representativeness of the dust sampling programs and possibly other factors. These factors are discussed later, when the exposure-response relationships of all available studies are compared (see Section 3.9). In the case of the two studies in Figure 3-1b, the form of the dose-response relationship is less clear, particularly for the group studied by Finkelstein (1983). The data from three other studies that provide dose-response information are not shown. In one (Weill et al., 1979), the dose-response relationship was affected by the large number of untraced individuals in the study; in two others of friction products manufacturing (Berry and Newhouse, 1983; McDonald et al., 1984), the relationship was too weak to provide any guidance as to its form. (These three studies are considered later, in Section 3.9.) In one case, when exposure-response relationships were analyzed according to both duration and intensity of exposure (McDonald et al., 1980), the results were less dramatic than shown in Figure 3-1a. However, this may be the result of small numbers; only 46 excess lung cancer deaths are reported in all exposure categories.

In the discussion of the time relationship of lung cancer risk and asbestos exposure, the data can be interpreted in terms of a multistage model of cancer in which asbestos appears to act at a single late stage. The continued high risk following cessation of exposure results from the continued presence of asbestos in the lungs. This model is compatible with a linear dose-response relationship and with the synergistic interaction between asbestos and cigarette smoking.

Fewer data are available on the exposure-response relationship for mesothelioma. Table 3-3 lists the mesothelioma mortality from four studies (Seidman, 1984; Hobbs et al., 1980; Jones et al., 1980; Finkelstein, 1983) in terms of cases per 1000 person-years of observation or percentage of mesothelioma deaths. The data of Seidman are presented both in terms of duration of employment and estimated cumulative fiber exposure. The exposure circumstances of

TABLE 3-3. THE RISK OF DEATH FROM MESOTHELIOMA ACCORDING TO THE TIME OF ASBESTOS EXPOSURE, IN FOUR STUDIES

Study	Exposure period (months unless noted)	Number of deaths	Estimated person-years (10+ years from first exposure)	Deaths/ 1000 person-years	Number exposed	Percent of deaths
Hobbs et al. (1980)						
	<3	0	21,213	0		
	3 - 11	10	19,548	0.5		
	12+	16	14,833	1.1		
Jones et al. (1980)						
	<5	0			314	0
	5 - 10	3			116	2.6
	10 - 20	4			145	2.8
	20 - 30	4			101	4.0
	30+	5			51	9.8
Seidman (1984)						
	2.2	1	3,700	2.7		
	7.1	5	1,203	4.2		
	15.4	4	1,263	3.2		
	57	7	1,248	5.6		
	8.8[a]	2	4,104	0.5		
	37.5[a]	5	1,162	4.3		
	75[a]	6	1,053	5.7		
	125[a]	2	420	4.8		
	200[a]	1	425	2.4		
	375[a]	1	250	4.0		
Finkelstein (1983)						
	44	1		1.9		
	92	2		4.9		
	180	6		11.9		

[a] Exposure in fiber-years/ml.

the groups studied by Jones et al. (1980) and Seidman (1984) offer the ideal circumstances for studying the effects of cumulative exposure on risk. The average exposure duration of each group was short (less then two years) and all individuals began exposure at approximately the same time during World War II. Thus, the confounding effect of time on the observed risk 20 or more years from onset of exposure is largely removed. To the extent that the distributions in duration and time from onset of employment are similar in the different exposure categories of Finkelstein (1983) and Hobbs et al. (1980), the data would reflect an exposure-response relationship. This is likely to be approximately correct, but direct information is not available.

Figure 3-2 displays the data of Table 3-3. To the extent that duration of employment is related to dose, the studies of Jones et al. (1980) and Hobbs et al. (1980) are compatible with a linear dose-response relationship, as is that of Finkelstein (1983). The study of Seidman (1984) is highly non-linear, especially when mesothelioma risk is plotted against estimated dose in f-y/ml. The relationship, however, is supralinear (i.e., one involving fractional powers of dose). This is likely to be the result of statistical uncertainties associated with small numbers rather than exposure misclassification; in the case of lung cancer a highly linear dose-response relationship was observed, albeit one that suggested a zero dose intercept at an SMR (standard mortality ratio) greater than 100.

Polynomials of degree one and two were fitted to the data of Jones et al. (1980), Hobbs et al. (1980), and Finkelstein (1983). The effect of including a quadratic term is shown in Table 3-4. In no case is a quadratic term required; in one case its coefficient is negative, indicating a supralinear relationship, and in the case where the effect is greatest (Finkelstein, 1983), the effect on the slope at zero dose is only a factor of 1.76. A quadratic term for the data of Seidman (1984) is clearly unwarranted.

A final study which provides some dose-response information is that of Newhouse and Berry (1979), which shows an increasing risk of mesothelioma with increasing duration and intensity of exposure (Table 3-5). However, a quantitative relationship cannot be determined.

Because of the limited dose-response data, the model for mesothelioma is not as well established as that for lung cancer. As will be seen, the time course of mesothelioma appears to be related only to the asbestos exposure. At this time, no interactive effects have been observed between asbestos and

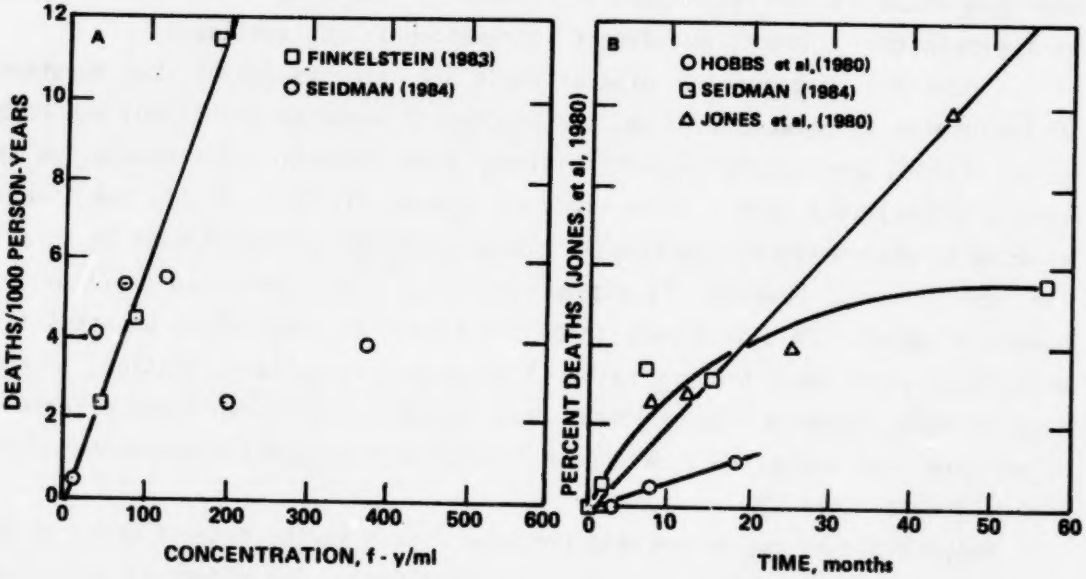

Figure 3-2. Exposure-response relationships for mesothelioma observed in four studies. Exposures are measured in terms of fiber per milliliter-years (f-y/ml) or duration of employment.

TABLE 3-4. ANALYSIS OF RESIDUALS IN POLYNOMIAL FIT TO OBSERVED MESOTHELIOMA DOSE-RESPONSE DATA

Study	Sum of Squares Accounted for by Linear term	Sum of Squares Accounted for by Quadratic term	Residual	Probability[a]	Ratio of slopes[b]
Hobbs et al., 1980	0.8133	0.0015	0.0067	0.72	0.85[c]
Jones et al., 1980	77.64	0.51	2.92	0.39	1.38
Finkelstein, 1983	78.50	1.19	0.27	0.28	1.76

[a] The probability that the observed deviation from linearity is by chance alone.

[b] The ratio of the slope of the dose-response function at zero dose without and with inclusion of a quadratic term.

[c] The sign of the quadratic term is negative indicating a supralinear relationship (i.e., one containing fractional powers of dose).

TABLE 3-5. RISK OF MESOTHELIOMA/100,000 PERSON-YEARS WITH INCREASING DURATION AND INTENSITY OF EXPOSURE (Newhouse and Berry, 1979)

	Duration of exposure	Deaths/100,000 Person-Years Intensity of Exposure Low-moderate[a]	Deaths/100,000 Person-Years Intensity of Exposure Severe[b]
Males	<2 yrs	33	104
	>2 yrs	93	243
Females	<2 yrs	{48}	136
	>2 yrs	combined	360

[a] 5-10 f/ml.

[b] >20 f/ml.

other agents in the etiology of the disease. The steep power law dependence of risk on time from asbestos exposure suggests that mesothelioma can be described within the framework of the multistage model (see Peto et al., 1982) and that asbestos may act early in the carcinogenic process. However, because asbestos has been shown to act late in the carcinogenic process in the case of lung cancer, it could do so also in the case of mesothelioma. If so, the dose-response relationship would involve higher than linear powers of dose.

While a quadratic component in the dose-response relationship has plausibility, the existing data provide no support for it. Further, the finding of mesothelioma among family contacts of workers suggests that a substantial risk exists at much less than occupational exposures among family contacts of chrysotile miners and millers and amosite factory workers. Among the miners and millers, 3 family member contact cases are known (McDonald and McDonald, 1980) compared to 12 among the miners and millers. For the amosite factory workers, there are 4 cases of family member contact mesothelioma compared to 15 cases due to occupational exposure (Anderson et al., 1976).

Even more limited data are available on a dose-response relationship for gastrointestinal (GI) cancer. As seen in Table 3-2, the strength of the evidence relating asbestos exposure to GI malignancy is less than that from lung cancer and mesothelioma; the excess relative risk, when present, is lower than that for lung cancer. Of the seven studies providing a clear dose-response relationship for lung cancer, information is available from six of them on a dose-response relationship for GI cancer. Weighted least squares regression analyses were run on the data of the studies. Table 3-6 lists the coefficients of these analyses, along with the standard errors of the slopes. As can be seen, five of the six studies which demonstrated a fairly steep dose-response relationship for lung cancer demonstrate a consistent and positive trend with exposure for GI cancer, but less strong than that for lung cancer. However, while indicating a positive trend with exposure, the data on GI cancer dose-response relationships are inadequate to establish the functional relationship between dose and risk.

This document uses a linear exposure-response relationship for estimating unit exposure risks for lung cancer and mesothelioma and for calculating risks at cumulative exposures 1/10 to 1/100 of those of the occupational circumstances of past years. It is a plausible relationship, and for lung cancer is strongly indicated by the existing evidence. While more limited data exist for mesothelioma, they also indicate a linear relationship. Its use has three distinct advantages: 1) point estimates of exposure-response can be made without knowledge of individual exposures, i.e., the excess mortality of an entire group can be related to the average exposure of the group; 2) extrapolation to various exposure circumstances can be made easily; and 3) it is likely to be a conservative extrapolation procedure from the point of view of human health. It is emphasized that linearity of exposure-response obtains only for similar times of exposure and observation among similarly aged individuals with similar personal habits.

TABLE 3-6. COMPARISON OF LINEAR WEIGHTED REGRESSION EQUATIONS FOR LUNG CANCER AND GI CANCER IN SIX COHORTS OF ASBESTOS-EXPOSED WORKERS

	Regression Equation[a]	
Study	Lung cancer	GI cancer
	Textiles	
Dement et al., 1983b	$\text{SMR} = 151 + 4.19(\pm 0.84)\text{f-y/ml}$[b]	$\text{SMR} = 34 + 1.18(\pm 0.62)\text{f-y/ml}$
McDonald et al., 1983a	$\text{SMR} = 110 + 2.07(\pm 0.25)\text{f-y/ml}$ $\%\text{RR} = 61 + 2.27(\pm 0.63)\text{f-y/ml}$[c]	$\text{SMR} = 113 + 0.59(\pm 0.37)\text{f-y/ml}$ $\%\text{RR} = 82 + 1.19(\pm 0.42)\text{f-y/ml}$
McDonald et al., 1983b	$\text{SMR} = 53 + 0.86(\pm 0.15)\text{f-y/ml}$ $\%\text{RR} = 70 + 1.20(\pm 0.33)\text{f-y/ml}$	$\text{SMR} = 82 + 0.42(\pm 0.19)\text{f-y/ml}$ $\%\text{RR} = 84 + 0.38(\pm 0.32)\text{f-y/ml}$
	Mining	
McDonald et al., 1980	$\text{SMR} = 92 + 0.043(\pm 0.008)\text{f-y/ml}$	$\text{SMR} = 88 + 0.011(\pm 0.010)\text{f-y/ml}$
	Manufacturing	
Seidman, 1984	$\text{SMR} = 325 + 2.72(\pm 0.54)\text{f-y/ml}$	$\text{SMR} = 110 + 0.084(\pm 0.43)\text{f-y/ml}$
Finkelstein, 1983	$\%\text{RR} = 100 + 4.79(\pm 2.70)\text{f-y/ml}$	$\%\text{RR} = 100 + 3.11(\pm 0.16)\text{f-y/ml}$

[a] Equations are calculated for the increased risk per f-y/ml of exposure. Data of McDonald et al., given in mppcf-y, were converted to f-y/ml using the relationship: 1 mppcf = 3 f/ml.

[b] ± standard error of the coefficient of f-y/ml.

[c] %RR is relative risk x 100.

3.6 TIME AND AGE DEPENDENCE OF LUNG CANCER

A relative risk model has long been assumed to be applicable for the description of the incidence of lung cancer induced by occupational asbestos exposure. Such a model is tacitly assumed in the description of mortality in terms of observed and expected deaths. Virtually every study of asbestos workers is described in these terms. Early suggestive evidence supporting it is found in the synergistic action between asbestos exposure and cigarette smoking (Selikoff et al., 1968), in which the lung cancer risk from asbestos exposure depended on the underlying risk in the absence of exposure. Relative risk models were discussed previously by Enterline (1976) and Peto (1977) and utilized in projections of lung cancer from past asbestos exposure by Nicholson et al. (1982). They were adopted in the risk analyses of the Advisory Committee on Asbestos (1979a,b), the U.S. Consumer Product Safety Commission (1983), and the National Academy of Sciences (1984). Information on lung cancer risk from exposures at different ages is now available from two studies (Selikoff et al., 1979; Seidman, 1984). The analyses of these data, along with the observations of linear dose-response relationships, provide substantial support for the use of such a formulation for lung cancer.

Information from the insulation workers study by Selikoff et al. (1979) on the time course of asbestos cancer risk is given in Figure 3-3, which shows the relative risk (here taken to be the ratio of observed to expected deaths) of death from lung cancer according to age for individuals first employed between ages 15 and 24 and for those employed between ages 25 and 34. The two curves rise with the same slope and are separated by the 10 years of difference in age at first exposure. This suggests that the relative risk of developing asbestos-related lung cancer according to time from onset of exposure is independent of age and of the pre-existing risk at the time of exposure. In contrast, both the slope and the value of the excess risk of lung cancer are two to four times greater for the group first exposed at older ages compared to those exposed at younger ages. The similarity of the data for each group in Figure 3-3 suggests that the data be combined and plotted according to time from onset of exposure. The result, shown in Figure 3-4, plots the data according to years from onset of exposure. However, because of the great stability of union insulation work, the curve also reflects effects according to duration of exposure up to at least 25 years from onset of exposure. A linear increase with time from onset of exposure occurs for about 35 years

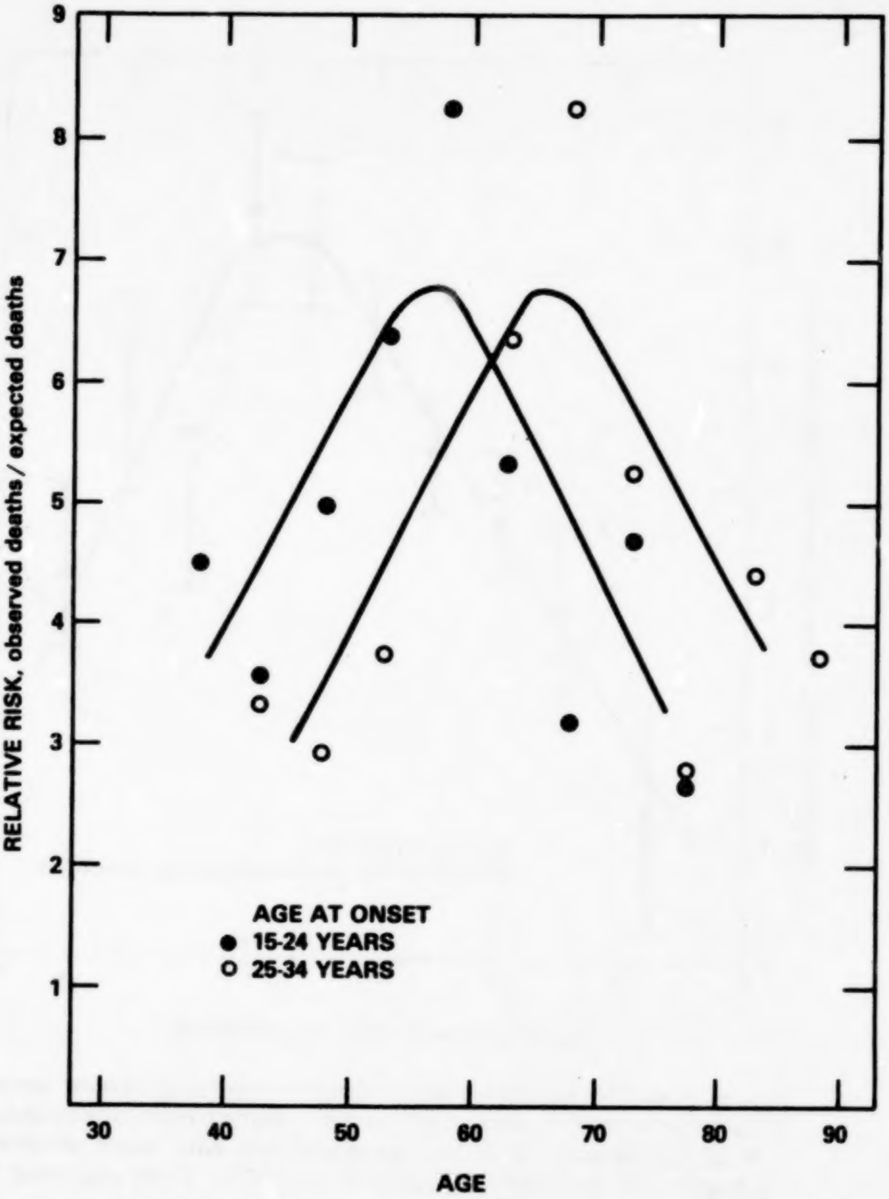

Figure 3-3. The relative risk of death from lung cancer among insulation workers according to age. Data supplied by I.J. Selikoff and H. Seidman.

Source: Nicholson (1982).

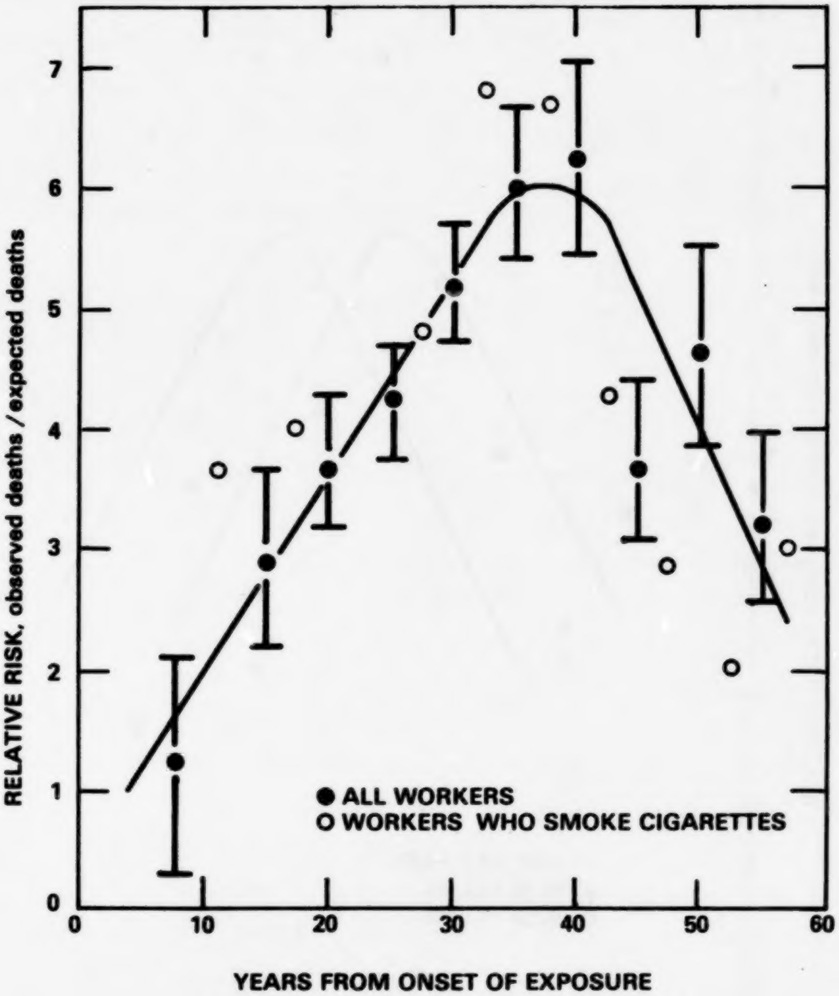

Figure 3-4. The relative risk of death from lung cancer among insulation workers according to time from onset of exposure (● all insulators; ○ indicates insulators who were smoking cigarettes at the start of follow-up in 1967.) Data supplied by I.J. Selikoff and H. Seidman.
Source: Nicholson (1982).

(to about the time when many insulation workers would have terminated employment), after which the relative risk falls substantially. The decrease is, in part, the result of the earlier deaths of smokers from the group under study due to their higher mortality from lung cancer and cardiovascular disease. However, the decrease is not solely the result of the deaths of smokers since a similar rise and fall occurs among those individuals who were smokers at the start of the study compared to smokers in the general population. Part of the decrease may relate to the elimination of asbestos, particularly chrysotile, from the lung; selection processes, such as differing exposure patterns (e.g., the survivors may have avoided intense exposures); or differing individual biological susceptibilities. While the exact reason for the effect is not understood, it is a general phenomenon seen in other mortality studies of asbestos workers (Nicholson, et al., 1979; 1985).

The early portions of the curves of Figures 3-3 and 3-4 have three important features. After a short delay, they show a linear increase in the relative risk of asbestos lung cancer according to time from onset of exposure. Figure 3-4 shows that this increased relative risk is proportional to the time worked, and, thus, to the cumulative asbestos exposure. However, the linear rise can occur only if the increased relative risk that is created by a given cumulative exposure of asbestos continues to multiply the underlying risk for several decades thereafter. Finally, an extrapolated linear line through the observed data points crosses the line of relative risk equal to one (that expected in an unexposed population) at between five and ten years from onset of exposure. This means that the increased relative risk appropriate to a given exposure is achieved soon after the exposure takes place. However, if there is a low underlying risk at the time of the asbestos exposure (as for individuals aged 20-30), most of the cancers that will arise from any increased risk attributable to asbestos will not occur for many years or even decades until the underlying risk becomes substantially greater.

The data of Seidman (1984) also show that exposure to asbestos multiplies the pre-existing risk of lung cancer and that the multiplied risk becomes manifest in a relatively short time. Figure 3-5 depicts the time course of lung cancer mortality beginning five years after onset of exposure of a group exposed for short periods of time. The average duration of exposure was 1.46 years; 77 percent of the population was employed for less than 2 years. Thus,

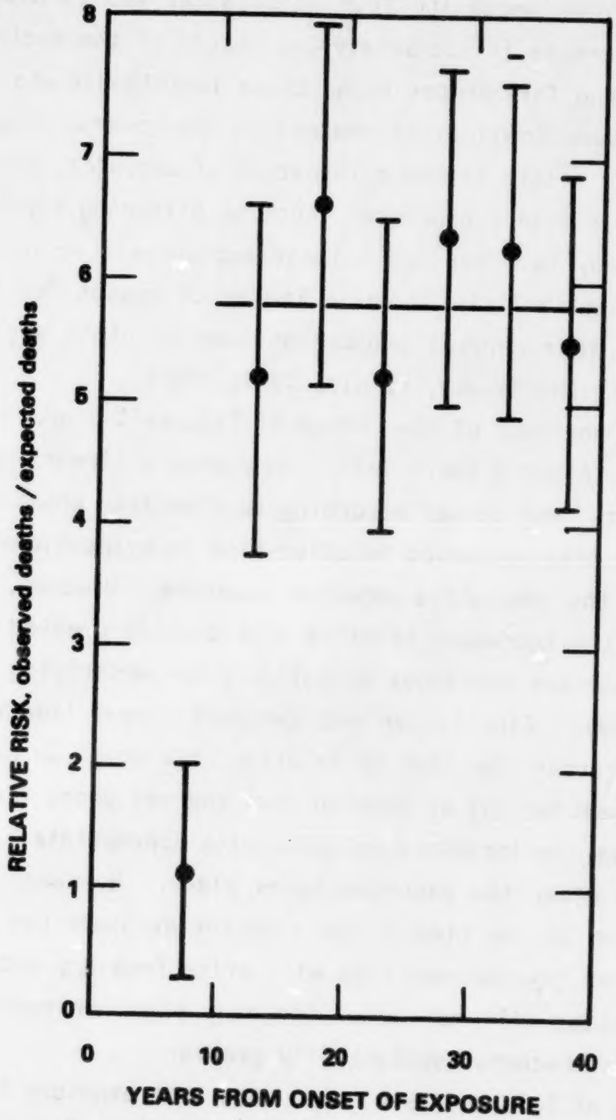

Figure 3-5. The relative risk of death from lung cancer (BE) among amosite factory workers according to time from onset of exposure.

Source: Seidman (1984).

exposure had largely ceased prior to the beginning of the follow-up period. A rise to a significantly elevated relative risk occurred within ten years and remained constant throughout the observation period of the study. Furthermore, the relative risk from a specific exposure is independent of the age at which exposure began, whereas the excess risk would have increased considerably with the age of exposure. Table 3-7 shows the relative risk of death from lung cancer for individuals exposed for less than and greater than 25 f-y/ml according to age at time of entrance into a ten-year observation period. Within a given age category, relative risk was similar during different decades from onset of exposure, as previously shown in Figure 3-5 with the overall data. However, relative risk also was independent of the age decade at entry into a ten-year observation period (see rows labeled "All" in each exposure category of Table 3-7). There is some reduction in the oldest, most heavily exposed group. This may be attributed to the same selection effects manifest at older ages in insulation workers.

In terms of carcinogenic mechanisms, it appears that asbestos acts largely like a lung cancer-promoting agent. However, because of the continued residence of the fibers in the lung, the promotional effect does not diminish with time after cessation of exposure as it may with chemical or tobacco promoters. Further, inhalation of the fibers can precede initiating events because many fibers remain continuously available in the lung to act after other necessary carcinogenic processes occur.

A feature of Figure 3-4 important in the assessment of asbestos carcinogenic risk is the decrease in relative risk after 40 years from onset of exposure, or 60 years of age. As mentioned previously, we do not have a full understanding of this decrease, but it generally applies. A virtually identical time course of lung cancer risk occurs in asbestos factory employees (Nicholson et al., 1985) and in Canadian chrysotile miners and millers (Nicholson et al., 1979). Because of the significant decrease at long times from onset of exposure and older ages, observations on retiree populations can seriously understate the actual risk of asbestos-related death during earlier years. To the extent that time periods between 25 and 40 years from onset of exposure are omitted from observation, a study will underestimate the full impact of asbestos exposure on death.

TABLE 3-7. RELATIVE RISK OF LUNG CANCER DURING 10-YEAR INTERVALS AT DIFFERENT TIMES FROM ONSET OF EXPOSURE

Years from onset of exposure	Age at start of period, years			
	40 - 49	50 - 59	60 - 69	70 - 79
	Less than 25 f-y/ml exposure			
5	0.0 [0.7][a]	1.4 (1)[b]	0.0 [4.1]	0.0 [0.7]
15	12.0 (3)	5.1 (4)	2.2 (3)	4.9 (5)
25	5.9 (1)	2.3 (2)	6.4 (9)	28.0 (3)
35	--	2.8 (1)	8.1 (6)	1.9 (1)
All	6.3 (4)	3.0 (8)	3.9 (18)	3.1 (9)
	Greater than 25 f-y/ml exposure			
5	0.0 [1.7]	12.9 (8)	6.6 (5)	3.7 (1)
15	7.7 (2)	11.1 (8)	5.6 (6)	6.2 (4)
25	25.0 (3)	9.7 (7)	12.0 (13)	2.1 (2)
35	--	4.3 (1)	4.0 (2)	8.8 (3)
All	8.3 (5)	10.5 (24)	7.6 (26)	4.5 (10)

[a] [] = no cases seen. Number of cases expected on the basis of the average relative risk in the overall exposure category.

[b] () = number of cases.

Source: Seidman (1984).

To appreciate the effect of the observed lung cancer time dependence upon the results of an epidemiological study, the excess risk of lung cancer was calculated for different observation periods for a hypothetical group exposed for 25 years beginning at age 20. The time course of the risk was set proportional to that of Figure 3-4 and 1978 general population rates were used. Table 3-8 lists the percent excess lung cancer mortality observed for three follow-up periods, 10 years, 20 years, and lifetime, beginning at different ages. As can be seen, the percent excess risk from start of exposure at age 20 to the complete death of all cohort members is 55 percent of the maximum. The percent excess risk increases up to age 50 as the follow-up period starts later, reflecting the increased relative risk concomitant with increased exposure. For observations starting after age 50 it falls substantially; follow-up begun at age 65 observes only 38 percent of the full risk. To the extent that a group under observation has an age distribution that is similar

TABLE 3-8. ESTIMATES OF THE PERCENTAGE OF THE MAXIMUM EXPRESSED EXCESS RISK OF DEATH FROM LUNG CANCER FOR A 25-YEAR EXPOSURE TO ASBESTOS BEGINNING AT AGE 20[a]

Age at start of observation, years	Period of follow-up, years			Years from onset of exposure
	10	20	Lifetime	
20	2	32	55	0
30	34	65	55	10
40	69	91	56	20
50	97	81	55	30
60	73	55	46	40
65	55	41	38	45
70	37	29	29	50

[a] The maximum expressed risk is that manifest 7.5 years after the conclusion of the 25-year exposure.

to the number alive in each quinquennium in a lifetime follow-up, an observation for any period of time would reflect the same mortality ratio as an observation from onset of exposure to the death of the total cohort.

The data in Table 3-8 came from observations on long-term exposures to high concentrations of asbestos (>10 f/ml) where preferential death of susceptible individuals occurred. Thus, appropriate comparisons between heavily exposed groups could be made on the basis of lifetime risk (i.e. 55 percent of the maximum), as well as on the maximum risk. However, in groups exposed to low levels (<0.1 f/ml), even for many years, selection effects may be much less important. A minimal excess risk would barely affect the pool of susceptible individuals. A lesser effect would also be expected from short-term exposures (to less than extreme concentrations). If selection effects are largely the cause of the disease, the maximum expressed relative risk would be most appropriate for estimating risks associated with low-level exposures. However, if the decrease is largely the result of elimination of asbestos from the lung or the biological neutralization of deposited fibers, a decrease in relative risk beginning at about 35 years from onset of exposure should be considered. This is discussed in Chapter 6.

The above discussion supports a general model for lung cancer in which the asbestos-related risk, t years from onset of exposure, is proportional to the cumulative exposure to asbestos at time t-10 years multiplied by the age and the calendar year risk of lung cancer in the absence of exposure. The incidence of lung cancer can be expressed formally by

$$I_L(a,y,t,d,f) = I_E(a,y)\ [1 + K_L \cdot f \cdot d(t-10)] \qquad (3\text{-}3a)$$

Here, $I_L(a,y,t,d,f)$ is the lung cancer incidence observed or projected in a population of age, a, observed in calendar period, y, at t years from onset of an asbestos exposure of duration, d, and average intensity, f. $I_E(a,y)$ is the age and calendar year lung cancer incidence expected in the absence of exposure. If smoking data are available, I_L and I_E can be smoking-specific incidences. f is the intensity of asbestos exposure to fibers longer than 5 μm/ml (f/ml), d is the duration of exposure up to 10 years from observation, and K_L is a proportionality constant that is a measure of the carcinogenic potency of the asbestos exposure. A delay in manifestation of risk is based on the data of Seidman (1984) and Selikoff et al. (1979); in neither study was any excess lung cancer seen prior to 10 years from onset of exposure. From Equation 3-3a, the relative risk of lung cancer, I_L/I_E, is independent of age and depends only on the cumulative exposure to asbestos.

Different asbestos varieties have different size distributions, and the fraction greater than 5 μm depends on fiber type and the production process (Nicholson et al., 1972; Gibbs and Hwang, 1975). Animal data demonstrate that dimensions (length and width) are important variables in fiber carcinogenicity. Thus, K_L would be expected to depend on fiber type and fiber dimension. In practice, however, uncertainties in establishing quantitative dose-response relations, through the application of Equation 3-3a to observed data, may preclude the determination of K_L by fiber type (see Section 3.17).

3.7 MULTIPLE FACTOR INTERACTION WITH CIGARETTE SMOKING

The multiplicative interaction between asbestos and the underlying risk of lung cancer is seen in the synergism between cigarette smoking and asbestos exposure, first identified by Selikoff et al. (1968). Later data on U.S. insulation workers confirm and extend the initial findings (Hammond et al., 1979a): In this larger study, 12,051 asbestos workers, 20 or more years from onset of their exposure, were followed from 1967 through 1976. At the outset, 6841 volunteered a history of cigarette smoking, 1379 said they had not smoked cigarettes, and the rest provided no information. By January 1, 1977, 299 deaths had occurred among the cigarette smokers and 8 among those not reported as smokers.

This experience was compared to an age- and calendar year-specific basis with that of like men with the same smoking habits in the American Cancer Society's prospective Cancer Prevention Study (Hammond, 1966). For the control group, 73,763 white males who were exposed to dusts, fumes, gases, or chemicals at non-farming work were selected. The age standardized rates per 100,000 person-years for each group are shown in Table 3-9. The results show that both the smoking and non-smoking lung cancer risks are multiplied five times by the worker's asbestos exposure. However, since the risk is low for non-smokers, multiplying it five times does not result in many cases, although any excess is clearly undesirable. On the other hand, smoking by itself causes a major increase and when that high risk is then multiplied five times, an immense increase is found. Corroborative data on the multiplicative smoking-asbestos interaction are seen in studies by Berry et al. (1972), McDonald et al. (1980), and Selikoff et al. (1980). However, these do not show as exact a multiplicative effect as that of Hammond et al. (1979a).

TABLE 3-9. AGE-STANDARDIZED LUNG CANCER DEATH RATES FOR CIGARETTE SMOKING AND/OR OCCUPATIONAL EXPOSURE TO ASBESTOS DUST COMPARED WITH NO SMOKING AND NO OCCUPATIONAL EXPOSURE TO ASBESTOS DUST

Group	Exposure to asbestos?	History cigarette smoking?	Death rate[a]	Mortality difference	Mortality ratio
Control	No	No	11.3	0.0	1.00
Asbestos Workers	Yes	No	58.4	+47.1	5.17
Control	No	Yes	122.6	+111.3	10.85
Asbestos Workers	Yes	Yes	601.6	+590.3	53.24

[a] Rate per 100,000 person-years standardized for age on the distribution of the person-years of all the asbestos workers. Number of lung cancer deaths based on death certificate information.

Source: Hammond et al. (1979a).

The study by Hammond et al. (1979a) also carried the asbestos-smoking interaction a step further, to show increased risk of death from asbestosis. As noted previously, insulation work carries a risk of fatal progressive pulmonary fibrosis, and some of those who never smoked cigarettes died of asbestosis. Nevertheless, asbestosis mortality for men who smoked a pack or more a day was 2.8 times higher than for men who never smoked regularly. Cigarette smoking, with resulting bronchitis and emphysema, adds an undesirable and sometimes unsupportable burden to the asbestos-induced pneumoconiosis. Interactive effects between cigarette smoking and the prevalence of X-ray abnormalities were reported previously (Weiss, 1971). However, no relationship was found in the Hammond et al. (1979a) study (Seidman, quoted in Frank, 1979) between cigarette smoking and the risk of death from mesothelioma or gastrointestinal cancer.

3.8 METHODOLOGICAL LIMITATIONS IN ESTABLISHING DOSE-RESPONSE RELATIONSHIPS

There are substantial difficulties in establishing dose-response relationships for human exposure to asbestos, perhaps the most important being that current health effects are the result of exposures to dust in previous decades when few and imperfect measurements of fiber concentrations were made. Current estimates of what such concentrations might have been can be inaccurate, since individual exposures were highly variable. Further, while disease response now can be established through epidemiological studies, these, too, can be misleading because of methodological limitations. Despite this difficulty, useful estimates of risk can be made to provide an approximate measure of asbestos disease potential in environmental circumstances. Limitations of existing data can be taken into account and their recognition can stimulate appropriate research to fill identified gaps.

One of the important limits on the accuracy of exposure-response data for asbestos diseases is our lack of information concerning past fiber exposures of those populations whose mortality or morbidity have been evaluated. Few measurements were made in facilities using asbestos fibers prior to 1965, and those measurements that were done quantified all dust (both fibers and particles) present in the workplace air. Current techniques, using membrane filters and phase contrast microscopy for the enumeration of fibers longer than 5 μm, have been utilized in Great Britain and the United States only since 1964 (Ayer et al., 1965; Holmes, 1965). They have been standardized in the United States only since 1972 (National Institute for Occupational Safety and Health, 1972; Leidel et al., 1979), and even later in Great Britain.

Modern counting techniques may be utilized to evaluate work practices and ventilation conditions believed to be typical of earlier activities. However, it is always difficult to duplicate materials and conditions of earlier decades so that such retrospective estimates are necessarily uncertain. Alternatively, fiber counting techniques using the particle counting instrumentation of earlier years can be used now to evaluate a variety of asbestos-containing aerosols. The comparative readings would then serve as a "calibration" of the historic instrument in terms of fiber concentrations. Unfortunately, the calibration depends on the type and size distribution of the asbestos used in the process under evaluation and on the quantity of other dust present in the aerosol. Thus, no universal conversion has been found between earlier dust measurements and current fiber counts.

In the United States and Canada, those few data that were obtained on asbestos workers' exposures prior to 1965 are based largely upon total dust concentrations measured using a midget impinger. Fibers were inefficiently counted with this instrument because of the use of bright field microscopy. Attempts to compare fiber concentrations with midget impinger particle counts generally showed poor correlations (Ayer et al., 1965; Gibbs and LaChance, 1974) (e.g., see Figure 3-6). In the United Kingdom, the thermal precipitator was used from 1951 through 1964 in one plant for which environmental data have been published. This instrument, too, does not allow accurate evaluation of fiber concentrations. The variability in the correlation between fiber measurements and thermal precipitator data is reported to be large (Steel, 1979), but no specific data are given. Finally, both the midget impinger and the konimeter were often used as area rather than personal samplers. Sources of dust were often sampled for control purposes, even though no personnel were directly exposed.

Even with the advances in fiber counting techniques, significant errors may be introduced into attempts to formulate general fiber exposure-response relationships. The convention now in use, that only fibers longer than 5 μm be counted, was chosen solely for the convenience of optical microscopic evaluation (since surveillance agencies are generally limited to such instrumentation). It does not necessarily correspond to any sharp demarcation of effect for asbestosis, lung cancer, or mesothelioma. While it is readily

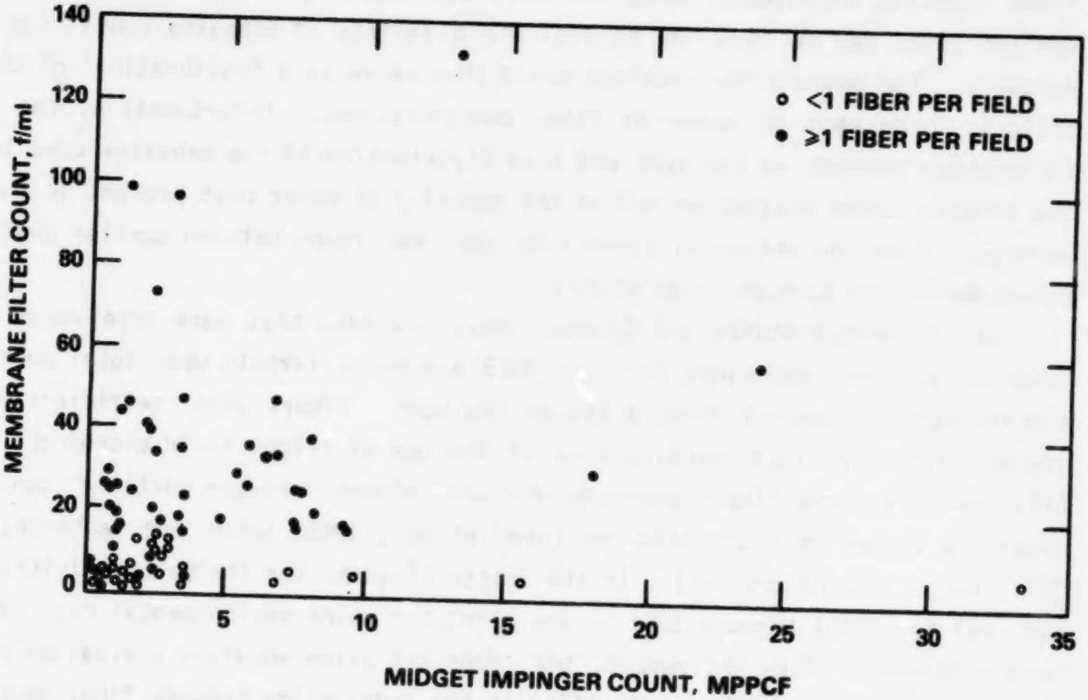

Figure 3-6. A plot of membrane filter and midget impinger counts; MPPCF represents millions of particles per cubic foot. Source: Gibbs and LaChance (1974).

understood that counting only fibers longer than 5 μm enumerates just a fraction of the total number of fibers present, there is incomplete awareness that the fraction counted is highly variable, depending upon the fiber type, the process or products used, and even the past history of the asbestos material (e.g., old versus new insulation material), among other factors. For example, the fraction of chrysotile fibers longer than 5 μm in an aerosol can vary by a factor of 10 (from as little as 0.5 percent of the total number to more than 5 percent). When amosite aerosols are counted, the fraction longer than 5 μm may be 30 percent, extending the variability of the fraction counted to two orders of magnitude (Nicholson et al., 1972; Nicholson, 1976a; Winer and Cossette, 1979).

Even if consideration is restricted to fibers longer than 5 μm, many fibers are missed by optical microscopy. Using electron microscopy, Rendall and Skikne (1980) measured the percentage of fibers with a diameter less than 0.4 μm (the approximate limit of resolution of an optical microscope) in various asbestos dust samples. In general, they found that more than 50 percent of the 5 μm or longer fibers are less than 0.4 μm in diameter and, thus, are not visible using a standard phase contrast optical microscope. Moreover, as with length distribution, diameter distribution varies with activity and fiber type. As a result, the fraction of fibers longer than 5 μm visible by light microscopy varies from about 22 percent in chrysotile and crocidolite mining and amosite/chrysotile insulation manufacturing to 53 percent in amosite mining. Intermediate values of 40 percent are measured in chrysotile brake lining manufacturing and 33 percent in amosite mill operations. Thus, even perfect measurement of workplace air, with accurate enumeration of fibers according to currently accepted methods, would be expected to lead to different exposure-response relationships for any specific asbestos disease when different work environments are studied. Conversely, risks estimated for a given exposure circumstance must have a large range of uncertainty to allow for the variability resulting from fiber size effects.

Those uncertainties in the physical determinations of past fiber concentrations and the difficulty in evaluating the exposure parameter of importance in current measurements are exacerbated by sampling limitations in determining individual or even average exposures of working populations; only few workmen at a worksite are monitored, and then only occasionally. Variability in work practices, ventilation controls, use of protective equipment, personal habits, and sampling circumstances add considerable uncertainty to our knowledge of exposure.

Statistical variability associated with small numbers and methodological difficulties in the estimation of disease also are important contributions to the variability in exposure-response relationships. Studies can be significantly biased by inclusion of recently employed workers in study cohorts, use of short follow-up periods, and improper treatment of the various time factors that are important in defining asbestos cancer. Particularly, inadequacies of tracing, can lead to significant misestimates of disease. Generally, 10 percent to 30 percent of an observation cohort will be deceased (sometimes even less). If 10 percent of the group is untraced and most are deceased, very large errors in the determination of mortality could result, even if no person-years are attributed to the lost-to-follow-up group. Finally, the choice of comparison mortality rates can introduce substantial errors. Local rates are generally the most desirable to use, but these may be unstable because of small numbers, or they may be affected by special circumstances (e.g., other industry). Data on general population worker mortality rates are not available, and existing general population rates may overstate the expected total mortality due to a "healthy worker effect" (Fox and Collier, 1976). Proper consideration of smoking habits is important in the determination of lung cancer risks. Unfortunately, full information on the smoking patterns of all individuals in a cohort is often not available.

3.9 QUANTITATIVE DOSE-RESPONSE RELATIONSHIPS FOR LUNG CANCER

In concept, exposure-response relationships can best be determined from studies in which individual exposures are estimated for each cohort member, subgroups are established according to cumulative exposure (with proper consideration of time factors), and an exposure-response relationship is determined from effects observed in all exposure categories. Consistencies in the observed exposure-response relationships, and an appropriate intercept at zero exposure, strengthen the risk estimates made from such studies. Dose-response relationships are commonly obtained by two methods. One method utilizes mortality rates in a comparison population (usually the general population of the same area) with standard mortality ratio (SMR) calculated for each exposed subgroup by multiplying the ratio of observed to expected deaths by 100. Crucial to the validity of the calculation is the choice of comparison rates.

Ideally, exposures to confounding factors, such as from cigarettes, should be the same in the study and comparison populations. The second method generates a relative risk (RR) factor at each exposure by a case-control anaylsis, where the number of cause-specific deaths is compared with the number of internal controls in each dose category. Such analysis is less subject to confounding factors in the comparison population, but has greater statistical variability.

In calculating a dose-response relationship, a weighted, rather than unweighted, least square analysis is most appropriate because there are large differences in the statistical validity of the individual SMRs or RRs in a given study. Values of K_L, the fractional increase in risk per unit exposure, can be calculated directly from the slopes of the regression lines of SMR or RR on dose (with a conversion, if necessary, from mppcf-y to f-y/ml).

Ideally, regression lines should pass through zero dose at an SMR of 100 or an RR of 1. The chances of this occurring are minimal. Statistical variability, even in the most ideal circumstances, will lead to intercepts different from that expected; in the case of SMRs, the comparison population may not be completely appropriate; incomplete tracing of a cohort can distort both SMRs and RRs; the comparison group in a relative risk analysis usually has some exposure; and finally, dose-response relationships can be affected by improper estimates of dose. It is important to identify the factor which may have led to an abnormal intercept, because it would indicate what adjustments might be made to the observed slope. For example, if improper comparison rates were used for the calculation of SMRs, and they were the sole cause of a higher or lower than expected intercept, it would be appropriate to divide both the slope and the intercept by the intercept/100 because the same percentage misestimate would be expected to exist in each exposure category. However, if the deviation from 100 were simply random, such division would compound what is already a statistical misestimate of the true slope. For example, if statistical variability led to an SMR intercept higher than 100, the observed slope would be less than the true slope. To divide by the intercept/100 would reduce it even further.

It may be difficult to identify misestimates of dose, especially within a single study. However, comparisons between estimates in similar exposure circumstances by different groups are useful in establishing the reasonableness of stated exposure estimates. In analyses of the available data on lung cancer risk for several studies, the uncertainties associated with response are greater than those associated with dose. This is particularly true in groups demonstrating low risks, where the difference between observed and expected deaths has an extremely large uncertainty relative to the difference.

Dose-response data can also be obtained using the overall SMR for a group and the average exposure for all cohort members. This calculation assumes that a linear dose-response relationship exists throughout the range of exposure and that the comparison population rates are appropriate to the study population. The first assumption would appear to be generally valid for lung cancer, but the second must be considered carefully in the analysis of each study. Such calculations will generally use Equation 3-3a, which is simplified as

$$I_L = I_E(1 + K_L \cdot f \cdot d) \qquad (3\text{-}3b)$$

Rearranging, one obtains

$$K_L = [(I_L - I_E)/I_E]/f \cdot d \qquad (3\text{-}3c)$$

or

$$K_L = [(I_L/I_E) - 1]/f \cdot d \qquad (3\text{-}3d)$$

$$= (\text{Relative Risk} -1)/\text{Cumulative Exposure}$$

Two approaches are possible in developing an exposure-response relationship for asbestos. One is to select the study or studies with the best exposure data, assuming an adequate measure of effect. The exposure-response relationship developed certainly would apply to similar exposure circumstances and may apply to others as well. Alternatively, all studies for which exposure-response information is available can be utilized along with estimates of the uncertainty of such data. An appropriate weighted average of the relationships found in different studies, taking into account observable differences in exposure circumstances, yields an overall exposure-response relationship. The former procedure has particular merit in evaluating the risk from an agent whose exposure can be well characterized, such as that from a single chemical species. However, this is not the case with asbestos where we are generally concerned with exposures to mixtures of different asbestos minerals. Even exposures to a single mineral species can involve substantially different fiber-size distributions which would strongly affect the carcinogenic potentials of the exposures. As mentioned above, a large fraction (usually greater than 50 percent) of the fibers longer than 5 μm are too thin to be visible by light microscopy. These thin and long fibers are the most carcinogenic in experimental studies (see Chapter 4) and are believed to be so in humans. The fraction of these uncounted fibers will vary with the particular process and a study or studies selected on the basis of the "best exposure measurements" may not be typical of most exposure circumstances in terms of its fiber-size distribution, even for one asbestos mineral. Thus, the quality of "good" exposure data for carcinogenic risk assessment may be illusionary.

The advantages of considering all studies for which exposure-response data can be developed are

1. any bias in the choice of studies selected for analysis is largely removed,
2. information can be obtained on the uncertainty of the estimate of an average value of K_L,
3. estimates of the effect of fiber type differences or process differences can be estimated better. Such information is of crucial importance and efforts to obtain it are warranted.

Primary among the disadvantages of the use of all exposure-response data is the fact that the quality of some of the data can only be estimated subjectively. The statistical variability in measures of response can be established quantitatively. However, biases in epidemiological studies may not be perceived and, of most importance, evaluations of the quality of exposure estimates are highly subjective, as are the estimates themselves.

Because of the above advantages, in the analysis that follows, all studies that provide exposure-response information are utilized. This procedure was also followed in the asbestos health effects reviews of the Consumer Products Safety Commission (1983) and the National Academy of Sciences (1983). In contrast, the recently published review by Doll and Peto (1985) for the British Health and Safety Commission selected two studies for analysis, based upon the quality of exposure measurements. These were the study by McDonald et al. (1983) of South Carolina textile workers and Peto et al.'s (1985) update of the mortality of Rochdale textile workers. As will be seen, their results are virtually identical to those obtained using all available studies.

In this document estimates of K_L are made from all sources of data within each study. If the data indicate that the results of a study are substantially affected by possible misestimates of exposure, that non-local rates are used for the expected mortality, or that inadequate tracing exists, an adjustment and its magnitude are clearly indicated. Consideration is made for deviations of the intercept of SMR regression lines from 100. However, if the source of the deviation cannot be identified, the slope as calculated is used.

For nine studies, values of K_L are estimated from a weighted linear regression analysis of the relationship between lung cancer risk and cumulative exposure. The weighting is the reciprocal of the variance of a particular data point. Perceived biases are taken into account and adjustments for them described in the text. Generally, the adjustment accounts for the difference in local lung cancer rates compared to those used in the published study. A value for K_L is calculated for each study using the slope of observed dose-response data, the slope of the odds ratios at different doses in case control analyses, or an average of the two procedures when both are done. In three studies, K_L is estimated from the difference in risk between heavily and lightly exposed groups (using individual exposure estimates) and/or the risk estimated from the ratio of overall excess lung cancer to the average exposure for the group. Finally, in one study, the relationship between SMR and duration of employment is used, assuming average group exposure per year of employment.

Table 3-10 shows the results of a variety of analytical procedures using the published data in 14 studies, along with 95 percent confidence limits calculated from the variance of the observed number of lung cancer cases and the slope of weighted regression lines. Adjustments for potential biases are shown as well as alternate regression analysis which either forces the regression line through an SMR of 100 at 0 dose or adjusts for a non-zero intercept by dividing by the intercept/100. It is emphasized that these two procedures can lead to misestimates of the actual exposure and increased uncertainty estimates. They are included, however, to provide a measure of the uncertainty that may be associated with regression analysis. Further, an analysis is shown in which the overall SMR and average exposure of the group was utilized to estimate the value of K_L. This analysis is particularly useful in estimating the range of uncertainty that may be present in given studies. For example, consider the study of Peto (1980). In the cohort exposed after 1950, 11 lung cancers were observed and 3.35 expected in the group followed 15 years after first employment and deemed to have a cumulative exposure of 200 f-y/ml. The excess risk is 7.65 cases, using Equation 3-3c, and K_L = (11 - 3.35)/3.35/200 = 0.0114 $(f\text{-}y/ml)^{-1}$. Assuming the number of deaths is an expression of a Poisson variate, the 95 percent confidence limit (from statistical considerations) will be from K_L = [0.0114 (5.4 - 3.35)]/7.75 to K_L = [0.0114 (19.7 - 3.35)]/7.75; i.e., from 0.0030 to 0.024.

The method for estimating K_L and the 95 percent confidence limit for each study is described in the text that follows. These data are listed in Table 3-10 and displayed in Figure 3-7. In addition to the statistical uncertainty listed in Table 3-10, the effect of a ± two-fold range of uncertainty in cumulative exposure is indicated in Figure 3-7 for most studies. This twofold range is a subjective choice, but is felt to be a realistic representation of the uncertainty in the cumulative exposure estimates from all the sampling problems mentioned previously. In some cases, for specific reasons listed, a greater exposure uncertainty is indicated. Even though response uncertainties and exposure uncertainties are unlikely to be correlated, the overall 95 percent confidence limit on a study is considered to be the sum of the listed exposure and response uncertainties.

3.9.1 Textile Products Manufacturing, United States (Chrysotile); Dement et al. (1982, 1983a, 1983b)

Mortality data from a chrysotile textile plant studied by Dement et al. (1982, 1983a, 1983b) allow a direct estimate of lung cancer risk per fiber exposure. Here, data from impinger measurements of total dust in terms of mppcf were available, characterizing dust concentrations since 1930. Further, 1106 paired and concurrent impinger-membrane filter measurements allow conversion of earlier dust measurements to fiber concentrations, suggesting that 3 f/ml is equivalent to 1 mppcf for all operations except fiber preparation. (The 95 percent confidence interval is 2-3.5 f/ml/mppcf.) A value of 8 f/ml/mppcf characterizes fiber preparation work (confidence interval, 5-9). Subsequent to 1940, average fiber concentrations in most operations are estimated to range from 5 to 10 f/ml, with the exception of fiber preparation and waste recovery where mean concentrations are 10-80 f/ml.

The study cohort consisted of all 1261 white males employed one or more months between January 1, 1940 and December 31, 1965. Vital status was determined for all but 26 individuals who were considered alive for purposes of analysis. SMRs for lung cancer were presented for five exposure categories in terms of cumulative fiber exposure (Table 3-11). A weighted regression line

TABLE 3-10. ESTIMATES OF THE PERCENTAGE INCREASE IN LUNG CANCER PER f-y/ml OF EXPOSURE (100 x K_L), ACCORDING TO DIFFERENT PROCEDURES IN 14 EPIDEMIOLOGICAL STUDIES

Study	Years from onset	Directly from weighted SMR regression	Adjusted for local rates or other factors (see text)	Adjusted to SMR = 100 at zero dose	SMR regression forced through 100 at zero dose	RR regression adjusted to RR = 1 at zero dose	Overall SMR-100 divided by average exposure	Adjusted for local rates or other factors (see text)	Adopted values and range
Dement et al., 1983b	15	4.19(±1.65)[a]	2.79(±1.10)	2.77(±1.08)	4.48(±1.10)		5.37 (2.94-8.45)	3.58 (1.99-5.63)	2.8 (1.7-5.6)
McDonald et al., 1983a	20	2.07(±0.50)	1.38(±0.33)	1.88(±0.45)	2.21(±0.39)	3.72(±2.04)	3.22 (1.46-4.95)	2.15 (0.97-3.30)	2.5 (1.0-3.7)
Peto, 1980	15						1.14 (0.30-2.41)		1.1 (0.30-2.4)[b]
McDonald et al., 1983b	20	0.86(±0.29)	1.06(±0.35)	1.62(±0.55)	0.41(±0.71)	1.71(±0.93)	0.10 (0.0-0.66) 0.87 (0.29-1.79)[c]	0.12 (0.0-0.81) 1.07 (0.36-2.21)	1.4 (0.36-1.7)
Berry & Newhouse, 1983	10					Negative	0.068 (0.0-0.52)		0.058 (0.010-0.80)
McDonald et al., 1984	20	Negative			0.13(±1.63)	0.003(±0.95)	0.79 (0.017-1.74) 0.085 (0.0-0.55)[d]		0.010 (0.010-0.55)
McDonald et al., 1980	20	0.043(±0.015)	0.064(±0.022)	0.047(±0.016)	0.035(±0.014)	0.057(±0.009)	0.045 (0.016-0.074)	0.064 (0.023-0.11	0.060 (0.023-0.11)
Nicholson et al., 1979	20	0.23(--)[e]	0.30(--)		0.30(--)		0.011 (0.043-0.21)	0.17 (0.064-0.32)	0.17 (0.064-0.32)
Rubino et al., 1979	20	0.51(--)[e]				0.89 (--)	0.013 (0.0-0.36)		0.075 (0.010-0.89)
Seidman, 1984	5	2.72(±1.06)		0.84(±0.33)	4.28(±2.27)		5.92 (4.49-7.36)		4.3 (0.84-7.4)
Selikoff et al., 1979	20	1.10(±0.097)	0.75(±0.066)				0.86 (0.75-0.97)	0.69 (0.60-0.78)	0.75 (0.60-1.1)
Henderson & Enterline, 1979	ret.[f]	0.34(±0.17)	0.49(±0.25)	0.24(±0.12)	0.43(±0.13)		0.046 (0.27-0.63)	0.67 (0.39-0.91)	0.49 (0.24-0.91)
Weill et al., 1979	20	0.31(±0.31)	0.53(±0.54)	0.42(±0.44)	0.22(±0.31)	0.35(±0.26)	0.041 (0.0-0.36) 0.034 (0.13-0.63)[g]	0.64 (0.0-1.1) 0.38 (0.14-0.70)	0.53 (0.14-1.1)
Finkelstein, 1983	20	Negative				4.80(±5.29)	6.70 (3.53-11.25)		6.7 (3.5-11.2)

[a] () = 95% confidence limits.

[b] Doll and Peto (1985) refer to an update of this study (Peto et al. 1985). They calculate values of 1.5 and 0.54 for 100 x K_L for workers first exposed after 1950 and after 1932, respectively.

[c] Calculated from highest exposure category.

[d] Calculated omitting lowest exposure category.

[e] Only two values.

[f] Retirees.

[g] Calculated from highest two exposure categories.

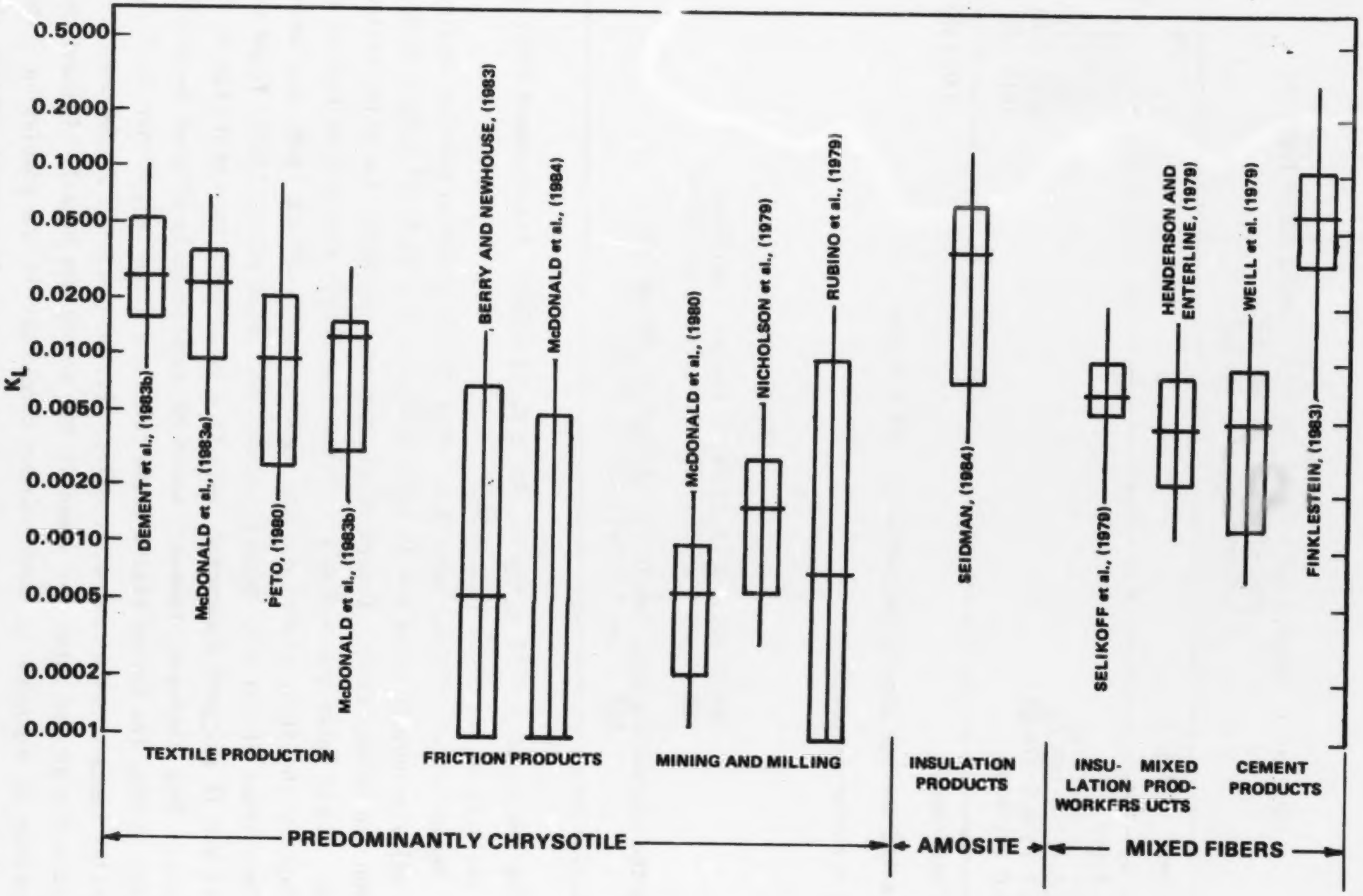

Figure 3-7. Values of K_L, the fractional increase in lung cancer per f-y/ml of exposure in 14 asbestos exposed cohorts. The open bar reflects the estimated 95% confidence limits associated with measures of response. The line represents the uncertainties associated with measures of exposure, generally ± a factor of two.

TABLE 3-11. LUNG CANCER RISKS, BY DOSE, AMONG SOUTH CAROLINA ASBESTOS TEXTILE WORKERS (Dement et al., 1983b)

Exposure in f-y/ml	SMR
1.4 (<2.74)	140 (5)[a]
15.1 (2.74-27.4)	279 (9)
68.5 (27.4-109.6)	352 (7)
191.8 (109.6-274.0)	1099 (10)
411.0 (>274.0)	1818 (2)
Complete cohort:	336 (33)

Estimated average cumulative exposure: 43.9 f-y/ml

[a] ( ) = number of deaths.

Regression equations

SMR = 150 + 4.19(±0.84) x f-y/ml weighted
SMR = 169 + 4.13(±0.32) x f-y/ml unweighted

Weighted regression equation forced through an SMR of 100
SMR = 100 + 4.48(±0.56) x f-y/ml

yields SMR = 150 + 4.19 x f-y/ml, for a K_L of 0.042. The standard error of the estimate of the slope is ± 0.84.

Dement et al. (1983b) uses U.S. rates for calculating expected deaths. Age-adjusted county rates are 75 percent higher, i.e $66.5/10^5$ versus $38.0/10^5$ (Mason and McKay, 1974). Dement et al. presents arguments for using national rates. Local rates are probably influenced by nearby shipyard employment (and perhaps by the study plant) and the smoking habits of the study population reflect those of the U.S. general population. Blot et al. (1979) found that World War II shipyard employment leads to a 60 percent increased risk of lung cancer. This increase, however, would be substantially diluted in county rates. Across the United States these rates are 11 percent higher in shipyard counties compared with control counties. Further, Acheson and Gardner (1983) point out that the rates for women in the county are equally high and they suggested an exposure to some unknown carcinogen in the population. The age-adjusted rates of contiguous counties are only 16 percent greater than those of the United States; those of the State of South Carolina are virtually identical to the United States rates.

It is unlikely that the origin of the high local rates will ever be resolved. As seen above, the SMR at zero exposure is calculated to be 150 from the weighted regression analysis. We will use this value as a measure of possible overestimates of the SMRs at all exposures, and we will divide the value of K_L above by 1.5. This brings the SMR at zero exposure to 100 and allows virtually full consideration that higher local rates are the appropriate comparison. (The remainder would be accounted for by shipyard employment.) The adjusted K_L is 0.028.

3.9.2 Textile Products Manufacturing, United States (Chrysotile); McDonald et al. (1983a)

Exposure-related mortality data at this same plant have recently been published by McDonald et al. (1983a). Their cohort consisted of all individuals employed for one or more months prior to January 1, 1959 and for whom a Social Security Administration (SSA) record existed. This eliminated from consideration individuals who began and ended their employment prior to mid-1937, when SSA numbers were first assigned. The same data used by Dement on past exposures were utilized to assign cumulative dust exposures, in mppcf-y, to each study participant. Male deaths, by cause, 20 years after first employment, are related to dust exposure accumulated to 10 years prior to death. Data for lung cancer are shown in Table 3-12. A weighted regression analysis yields the relation SMR = 110 + 6.22 mppcf-y. No data are given by McDonald et al. (1983a) on cumulative fiber exposures. If we use the average relationship found by Dement et al., 1 mppcf = 3 f/ml, we obtain a K_L of 0.021. Adjusting by the value 1.5, as above, to account for the higher local rates, yields a K_L of 0.014. (McDonald et al. (1983a) used South Carolina rates rather than local rates).

McDonald et al. (1983a) also made estimates of risk using a Mantel and Haenszel (1959) case-control analysis, as in Table 3-12. A weighted regression line yields a slope of 0.068. Because the RR regression was obtained using internal controls, no adjustment for local rates is necessary. However, since the controls were exposed, the zero dose intercept should be used as the measure of risk in an unexposed group. This requires dividing the slope by the intercept to obtain an adjusted regression line. Dividing by the zero exposure intercept, 0.61, and by 3 to convert to fiber exposures, gives a

TABLE 3-12. LUNG CANCER RISKS, BY DOSE, AMONG SOUTH CAROLINA ASBESTOS TEXTILE WORKERS (McDonald et al., 1983a)

Exposure in mppcf-y[a]	SMR	RR[b]
5 (<10)	143.1 (31)[c]	1.00 (25)
15 (10-19)	182.7 (5)	0.98 (3)
30 (20-39)	304.2 (8)	2.95 (8)
60 (40-79)	419.5 (7)	4.32 (7)
120 (≥80)	1031.9 (8)	15.00 (6)
Complete cohort:	199.5 (53)	

Estimated average cumulative exposure: 10.3 mppcf-y.

[a] Exposure accumulated to 10 years before death.

[b] Relative risk from an internal case-control analysis.

[c] ( ) = number of deaths.

Regression equations

SMR = 110 + 6.22(±0.76) x mppcf-y weighted
SMR = 63 + 7.68(±0.76) x mppcf-y unweighted

RR = 0.61 + 0.068(±0.019) x mppcf-y weighted
RR = -0.80 + 0.123(±0.017) x mppcf-y unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 6.63 (±0.61) x mppcf-y

value of $K_L = 0.037$. We will use 0.025, the average of 0.014 and 0.037, to represent this study. The agreement with the results of Dement et al. (1982, 1983a,b) is very good.

3.9.3 Textile Products Manufacturing, Rochdale, England (Chrysotile); Peto (1980)

Table 3-13 shows the lung cancer and mesothelioma mortality experience from an often-studied British textile plant (Doll, 1955; British Occupational Hygiene Society, 1968; Berry et al., 1979; Knox et al., 1968; Peto, 1980; British Occupational Hygiene Society, 1983). The data are difficult to interpret because dust concentrations have changed fairly dramatically over the past five decades of plant operations, and so have subsequent estimates of

TABLE 3-13. MORTALITY EXPERIENCE OF 679 MALE ASBESTOS TEXTILE WORKERS (Peto, 1980)

Year first exposed	Period since first exposure (yrs)	Man-years	Lung cancer		Mesothelioma	
			0	E	0	rate per 10^3 p-y
1933-1950	10-14	1633	2	1.80	0	0.0
	15-19	1860	4	2.98	0	0.0
N = 424	20-24	1760	3	3.97	1	0.6
	25-29	1496	10	4.54	2	1.3
	30-34	837	8	3.14	2	2.4
	35-39	507	1	2.20	2	3.9
	Total	8093	28	18.63	7	-
1951 or later	10-14	1123	1	1.30	0	0.0
	15-19	1022	3	1.74	0	0.0
N = 255	20-24	556	7	1.31	0	0.0
	25-29	96	1	0.31	0	0.0
	Total	2797	12	4.65	0	-

those concentrations. No measurements of dust concentrations were made prior to 1951. Between 1951 and 1964, thermal precipitators were used to evaluate total dust levels; thereafter, filter techniques similar, but not identical, to those in the United States were used. Average fiber concentrations are published for earlier years based on a comparison of fiber counting with thermal precipitator techniques (Berry, 1973). Later these estimates were stated to be inaccurate; Berry et al. (1979) reported that a re-evaluation of the work histories indicated that some men had spent more time in less dusty jobs than previously believed and that previous average cumulative doses to 1966 had been overestimated by 50 percent.

Recently, as part of the British Government's review of its asbestos standard, the hygiene officers of the plant re-evaluated previously reported exposure data. It is now suggested that earlier static sampling methods underestimated personal exposures by a factor of about 2, and that whole field, rather than graticule field, microscopic counting understated fiber concentrations by another factor of 2 to 2.5 (Steel, 1979). In 1983, the

British Occupational Hygiene Society (1983) reported information on the differences between personal and static sampling. Data were presented for thirty-one simultaneous samples comparing the two techniques, the personal samplers indicating a greater fiber concentration in 22 cases. Using these data, the BOHS committee evaluated the cumulative fiber exposure (as of approximately 1976) for 284 individuals employed for 10 or more years subsequent to 1951. The overall average of the entire group was 182 f-y/ml. This is slightly less than the estimate of Peto (1980), who suggested that the exposure of 10+ years employees was 200-300 f-y/ml. However, Peto's estimate was based on preliminary data on only 126 men first employed between 1951 and 1955 (see Table 3-14).

These most recent estimates are clouded by questions concerning the appropriateness of multiplying static sampler concentrations by a factor approaching two. The BOHS data are directly contradicted by published data (See Table 3-15) from the factory on other comparisons of static and personal sampling results by job (Smither and Lewinsohn, 1973). Dr. Lewinsohn (1983) confirmed these results. He stated that the static sampler concentrations were generally higher than those of the personal samplers of men working at the monitored job. The company placed the static samplers to best reflect the breathing zone dust concentrations of machine operators while tending machines. Dr. Lewinsohn (1983) stated that if a machine were running smoothly, a worker would move away to the aisle adjacent to the machine from where he or she could continue to observe the operation and experience a lower dust concentration. The difference between static and personal sampling data appears to be greater in the dustier jobs. In the Rochdale factory, the average of the ratios of static to personal sample concentrations at the same work station is 1.8 (1.5 if the fiberizing operation is not considered). The recent comparison may not reflect the movement of a worker from his machine.

We will use a value of 200 f-y/ml to represent cumulative exposure of the post-1951 group fifteen or more years from onset of exposure, which probably overestimates the effective exposure of the group. While 200 f-y/ml, the average dose of all men employed 10 or more years, may underestimate the average total dose of men employed 15 or more years, it certainly overestimates the effective dose that accumulates to about 10 years prior to end of follow-up or death. As was shown above, this yields a K_L of 0.011. To reflect what could be a twofold lesser exposure, the upper exposure-related uncertainty in risk was increased from 2 to 4 in Figure 3-7.

TABLE 3-14. PREVIOUS AND REVISED ESTIMATES OF MEAN DUST LEVELS IN f/ml (WEIGHTED BY THE NUMBER OF WORKERS AT EACH LEVEL IN SELECTED YEARS)

	1936	1941	1946	1951	1956	1961	1966	1977	1974
Previous estimates corresponding to early fiber counts	13.3	14.5	13.2	10.8	5.3	5.2	5.4	3.4	-
Revised estimates corresponding to modern counting of static samples[a]	No measurements prior to 1951			32.4	23.9	12.2	12.7	4.7	1.1

[a] These estimates are based on preliminary data on 126 workers first employed between 1951 and 1955, and should be regarded as provisional.

Source: Peto (1980).

TABLE 3-15. DUST LEVELS: ROCHDALE ASBESTOS TEXTILE FACTORY, 1971

Department	Process	Static	Personal
Fiberizing	Bag slitting	3	1
	Mechanical bagging	4	1
Carding	Fine cards	3.5	2
	Medium cards	4.5	3.5
	Coarse cards	8	6
	Electrical sliver cards	1.5	1
Spinning	Fine spinning	2.5	3
	Roving frames	6	3
	Intermediate frames	5.5	3
Weaving	Beaming	0.5	0.5
	Pirn weaving	1.5	1
	Cloth weaving	2	1
	Listing weaving	0.5	0.5
Plaiting	Medium plaiting	4	2

Source: Smither and Lewinsohn (1973).

A second difficulty of the British textile factory study is that the dose-response data calculated from groups exposed before and after 1950 differ considerably. While no cumulative exposure data are published for the pre-1951 group, it is surprising that more disease is seen in the latter group, as the average intensity of exposure was certainly greater for the earlier group, perhaps by a factor of three. It is difficult to reconcile the differences between the two subcohorts employed in this facility. The data are severely limited by the relatively small size of the cohort and the few deaths available for analysis. Nevertheless, what would appear to be a nearly tenfold difference in the estimated risk of death from lung cancer suggests the possible existence of some unidentified bias in the pre-1951 group. The post-1950 group's mortality experience is more in accord with U.S. textile plants. The finding of only a 50 percent increase in lung cancer in exposure circumstances leading to 5.3 percent of deaths being from asbestosis is certainly unusual, as is the finding that there are as many mesotheliomas as excess lung cancers.

Doll and Peto (1985) recently reviewed the new information on the health effects of asbestos for the British Health and Safety Commission. Many of the above uncertainties, particularly that of the ratio of personal to static sampling counts, are discussed. A regression analysis of the ratio of personal to static counts against mean concentration indicated that the ratio is greater than one for concentrations less than 2 f/ml, but less than one for higher concentrations. Doll and Peto (1985) estimate values of K_L from the mortality in an expanded and updated study of the Rochdale cohort. Their results indicate K_L is 0.015 for workers first employed after 1950 and 0.0054 for all workers first employed after 1932.

3.9.4 Textile and Friction Products Manufacturing, United States (Chrysotile, Amosite, and Crocidolite); McDonald et al. (1983b); Robinson et al. (1979)

A plant located near Lancaster, Pennsylvania, which produced mainly textiles but also friction products and packings, was studied by Robinson et al. (1979), McDonald et al. (1983b), and earlier by Mancuso and Coulter (1963) and Mancuso and El-attar (1967). The plant, which began operations in the early 1900s, used between 3000 and 6000 tons of chrysotile per year over most of the period of its operation. Amosite constituted less than 1 percent of the fiber used, except for a three-year period, 1942 - 1944, when 375-600 tons of amosite were used in insulation blankets and mattresses. Crocidolite usage was approximately 3-5 tons per year (Robinson et al., 1979). The reports of

Robinson et al. (1979), Mancuso and Coulter (1963), and Mancuso and El-attar (1967) provide no information on the exposure of the cohort members to asbestos; so they cannot be used in establishing exposure-response relationships. In the study of McDonald et al. (1983b), dust concentrations, measured in mppcf, available from the 1930s through 1970 were used. However, no attempt was made to relate particle exposures to fiber exposures. The study cohort of McDonald et al. (1983b) comprised all individuals employed for one or more months prior to January 1, 1959 with their Social Security file identifiable in the Social Security Administration offices. These individuals were traced through December 31, 1977, and cause-specific mortality ratios, based on state rates, were related to cumulative dust exposure.

The results for lung cancer are shown in Table 3-16. The regression of SMR on dose has an unusually low intercept of 53. The overall SMR for lung cancer is also low. The low local rates (30.1 versus 37.7 for the state) (Mason and McKay, 1974) do not fully account for these deficits. Smoking histories are reported for only 36 individuals and indicate no unusual pattern. Because the full deficit cannot be explained, we have adjusted the slope by the ratio of the local to state lung cancer rates (0.81) rather than by 0.53, resulting in a slope of 0.032. The adjusted slope of the RR regression is 0.051. If these two values are averaged and a factor of 3 is used to convert from mppcf to f/ml, the exposure-response relationships give average K_L = 0.014. The factor of 3 was previously measured in textile manufacturing, the predominant activity in this plant. Calculating K_L using the overall SMR of the study suggests that the lower confidence limit of K_L is 0, but the SMR and RR regression lines strongly contradict this. Thus, for the lower confidence limit we will use a value calculated from the highest exposure relationship, where the uncertainty in comparison rates has less of an effect.

3.9.5 Friction Products Manufacturing, Great Britain (Chrysotile and Crocidolite); Berry and Newhouse (1983)

Berry and Newhouse analyzed the mortality of a large workforce manufacturing friction products. All individuals employed in 1941 or later were included in the study, and the mortality experience through 1979 was determined. Exposure estimates were made by reconstructing the work and ventilation conditions of earlier years. Fiber measurements from these reconstructed conditions suggested that exposures prior to 1931 exceeded 20 f/ml but those afterwards seldom exceeded 5 f/ml. From 1970, exposures were less than 1 f/ml.

TABLE 3-16. LUNG CANCER RISKS, BY DOSE, AMONG PENNSYLVANIA ASBESTOS TEXTILE AND FRICTION PRODUCTS WORKERS
(McDonald et al., 1983b)

Exposure in mppcf-y[a]	SMR	RR[b]
5 (<10)	66.9 (21)[c]	1.00 (20)
15 (10-19)	83.6 (5)	0.83 (4)
30 (20-39)	156.0 (10)	1.54 (10)
60 (40-79)	160.0 (6)	2.90 (6)
120 (>80)	416.1 (11)	6.82 (11)
Complete cohort:	105.0 (53)	

Estimated average cumulative exposure: 16.9 mppcf-y.

[a] Exposure accumulated to 10 years before death.
[b] Relative risk from an internal case-control analysis.
[c] ( ) = number of deaths.

Regression equations

SMR = 53 + 2.58(±0.45) x mppcf-y weighted
SMR = 41 + 2.94(±0.42) x mppcf-y unweighted

RR = 0.70 + 0.036(±0.010) x mppcf-y weighted
RR = 0.24 + 0.050(±0.005) x mppcf-y unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 1.22 (±1.07) x mppcf-y

These relatively low intensities of exposure kept the average cumulative exposure for the group to less than 40 f-y/ml.

The overall mortality of all study participants, 10 years and more after onset of exposure, was no greater than expected for all causes. Data for lung cancer are shown in Table 3-17. Cancer of the lung and pleura was slightly elevated in men (151 observed versus 139.5), but the excess was largely accounted for by eight mesothelioma deaths. No unusual mortality was found in those employed 10 or more years. Using a case-control analysis according to cumulative exposure, Berry and Newhouse (1983) estimated that the lung cancer increased risk was 0.06 percent per f-y/ml ($K_L = 0.00058$), with an upper 90 percent confidence limit of 0.8 percent per f-y/ml. Table 3-17 lists the results of the case control analysis. The weighted regression of RR on dose has a negative slope. The ratio of excess lung cancer to average group exposure yields a value of $K_L = 0.00068 = [(143/139.5)-1]/37.1$. We will use the value published by Berry and Newhouse, 0.00058, and their confidence limits for K_L.

TABLE 3-17. LUNG CANCER RISKS, BY DOSE, AMONG BRITISH ASBESTOS FRICTION PRODUCTS WORKERS
(Berry and Newhouse, 1983)

Exposure in mppcf-y	RR[a]
5 (0-9)	1.00 (50)[b]
30 (10-49)	0.79 (37)
75 (50-99)	0.86 (13)
200 (100-356)	0.88 (5)

Estimated average cumulative exposure: 31.7 f-y/ml.

[a] Relative risk from an internal case-control analysis.
[b] ( ) = number of deaths.

Regression equations

$$RR = 0.91 - 0.00076(\pm 0.0016) \times \text{f-y/ml weighted}$$
$$RR = 0.90 - 0.00019(\pm 0.00070) \times \text{f-y/ml unweighted}$$

3.9.6 Friction Products Manufacturing, United States (Chrysotile); McDonald et al. (1984)

McDonald et al. (1984) analyzed the mortality of the workforce employed in friction products production in the United States and attempted to relate it to cumulative dust exposure. However, a highly unusual mortality experience is observed. The overall mortality shows an elevated risk of death in the complete cohort for virtually all causes, largely confined to individuals employed for less than one year. The correlation of respiratory cancer SMR with cumulative dust exposure of those employed for more than one year shows little, if any, trend with increasing dust exposure, even though the overall SMR for lung cancer (see Table 3-18) is 137 for these individuals. The slopes of the regression equations of SMR on dose are slightly negative and those of relative risk are slightly positive. As with the McDonald et al. (1983b) Pennsylvania textile study, we will use the dose-response regression relationship for the measure of risk and set $K_L = 0.0001$ for this group. In Figure 3-7, this represents "zero" for the purpose of calculating geometric means.

TABLE 3-18. LUNG CANCER RISKS, BY DOSE, AMONG ASBESTOS FRICTION PRODUCTS PRODUCTION WORKERS
(McDonald et al., 1984)

Exposure in mppcf-y	SMR	RR[a]
5 (<10)	167.4 (55)[b]	1.00 (54)
15 (10-19)	101.7 (6)	0.40 (4)
30 (20-39)	105.4 (5)	0.91 (5)
60 (40-79)	162.8 (6)	1.40 (16)
120 (>80)	55.2 (1)	1.13 (1)

Complete cohort: 148.7 (73)

1+ yrs employment: 136.8 (49)

Estimated average cumulative exposure: 10.3 mppcf-y.

Estimated average exposure for
those employed more than 1 year: 15.5 mppcf-y.

[a] Relative risk from an internal case-control analysis.

[b] ( ) = number of deaths.

Regression equations

$$\text{SMR} = 160 - 0.85(\pm 0.52) \times \text{mppcf-y} \quad \text{weighted}$$
$$\text{SMR} = 147 - 0.62(\pm 0.46) \times \text{mppcf-y} \quad \text{unweighted}$$

$$\text{RR} = 0.69 + 0.00006(\pm 0.01) \times \text{mppcf-y} \quad \text{weighted}$$
$$\text{RR} = 0.78 + 0.0041(\pm 0.0039) \times \text{mppcf-y} \quad \text{unweighted}$$

Weighted regression equation forced through an SMR of 100:

$$\text{SMR} = 100 + 0.13\ (\pm 0.83) \times \text{mppcf-y}$$

The low value, however, is qualified by the overall high lung cancer mortality. As the origin of this elevated lung cancer mortality is workers employed for more than one year (where total mortality is close to that expected) is unknown, the upper limit of uncertainty will be given by the upper confidence limit on the ratio of lung cancer excess risk to average exposure in the 10-19 mppcf-y exposure groups. This procedure is similar to that used to estimate the lower confidence limit in the Pennsylvania textile cohort.

3.9.7 Mining and Milling, Quebec, Canada (Chrysotile); Liddell et al. (1977); McDonald et al. (1980)

The results reported by Liddell et al. (1977) and McDonald et al. (1980) on mortality (Table 3-19) according to total dust exposure in Canadian mines and mills can be converted to relationships expressed in terms of fiber exposures. SMR values are provided by McDonald et al. (1980) for various exposure categories in four different duration-of-employment categories. A weighted regression analysis of these data yields a relationship, SMR = 92 + 0.13 x mppcf-y. Using a value of 3 f/ml/mppcf for the particle fiber conversion factor yields a K_L of 0.00043. The factor of 3 f/ml/mppcf is the midpoint of the range of 1-5 f/ml/mppcf suggested by McDonald et al. as being applicable to most jobs in mining and milling. However, since McDonald et al. used the rates of the Province of Quebec for their comparison data, K_L is likely to be underestimated. In an earlier paper, McDonald et al. (1971) suggested that the lung cancer rates in the counties adjacent to the asbestos mining counties were about two-thirds those of the Province. This is substantiated by lung cancer incidence rates, in the Province of Quebec, published by Graham et al. (1977). These data for the years 1969-1973 are shown in Table 3-20 and confirm the earlier statement of McDonald et al. (1971). Thus, the above K_L will be multiplied by a factor of 1.5. Liddell et al. (1977) performed a case control analysis of the relative risk of lung cancer in this same period. Their regression equation suggests a K_L of 0.00057. We will use the average of these two estimates, 0.00060, for K_L.

The overall SMR of 125 based upon Quebec rates, for lung cancer mortality among all miners is surprising. In studies of the mortality of male residents of Thetford, in the midst of the Canadian asbestos mining area (Toft et al., 1981; Wigle, 1977), an SMR of 184 was seen for lung cancer and 230 for cancer of the stomach. Because no corresponding increases were seen in female cancer rates, Toft et al. (1981) and Wigle (1977) attributed the excesses to occupational exposure in the mines. Siemiatycki (1982) presented data on the mortality of male residents of Asbestos and Thetford Mines, Quebec, that indicated an SMR for lung cancer of 148 compared to Quebec rates. The origin of a lower SMR for those employed in mining and milling compared to all male residents could result from the departure of most short-term workers from the area, but data on this possibility are lacking. While the risk appears low compared to town mortality, the agreement between the SMR and RR analyses is very good.

TABLE 3-19. LUNG CANCER RISKS, BY DOSE, AMONG CANADIAN CHRYSOTILE ASBESTOS MINERS

McDonald et al., 1980 in mppcf-y	SMR	Liddell et al., 1977 Exposure in mppcf-y	RR[a]
< 1 year of employment			
.5	117 (19)[b]	3 (<6)	1.00 (43)
1.7	91 (12)	8 (6-10)	1.07 (10)
5.8	88 (9)	20 (10-30)	0.96 (24)
39.0	80 (7)	65 (30-100)	1.16 (37)
		200 (100-300)	1.22 (31)
1 to 4.9 years of employment		450 (300-600)	1.88 (27)
		800 (600-1000)	2.39 (18)
3.3	66 (5)	1250 (1000-1500)	3.49 (10)
13.6	95 (13)	1750 (1500-2000)	4.97 (6)
59.0	82 (6)	3000 (2000+)	5.42 (9)
231.3	78 (5)		
5 to 19.9 years of employment			
16.0	141 (13)		
58.2	122 (14)		
178.5	83 (7)		
704.0	217 (16)		
20+ years of employment			
104.6	121 (28)		
261.3	108 (20)		
549.1	220 (24)		
1141.4	265 (32)		

Complete cohort: 125 (230)

Estimated average cumulative exposure: 185 mppcf-y.

[a] Relative risk from an internal case-control analysis.

[b] ( ) = number of deaths.

Regression equations

$$\mathrm{SMR} = 92 + 0.13(\pm 0.024) \times \text{mppcf-y} \quad \text{weighted}$$

$$\mathrm{SMR} = 93 + 0.13(\pm 0.024) \times \text{mppcf-y} \quad \text{unweighted}$$

$$\mathrm{RR} = 0.99 + 0.0017(\pm 0.00013) \times \text{mppcf-y} \quad \text{weighted}$$

$$\mathrm{RR} = 1.10 + 0.0017(\pm 0.00013) \times \text{mppcf-y} \quad \text{unweighted}$$

Weighted regression equation forced through an SMR of 100:

$$\mathrm{SMR} = 100 + 0.12\ (\pm 0.02) \times \text{mppcf-y}$$

TABLE 3-20. LUNG CANCER INCIDENCE RATES IN URBAN AND RURAL AREAS OF QUEBEC PROVINCE, 1969-1973

	MALES		FEMALES	
Region	Rate	Population	Rate	Population
Asbestos counties	33.59	57,685	4.39	57,630
Peripheral counties	23.71	209,320	4.64	210,180
Other rural	27.29	1,295,895	3.87	1,264,795
Montreal	48.67	1,222,245	8.70	1,281,865
Quebec City	50.53	204,435	6.96	218,745
Province	37.47	2,989,580	6.20	3,033,215
Ratio: Rural/Province	.728		.624	
Ratio: Peripheral/Province	.633		.748	

From: Graham et al. (1977).

3.9.8 Mining and Milling, Thetford Mines, Canada (Chrysotile); Nicholson (1976b); Nicholson et al. (1979)

Somewhat higher risks in the mining industry were obtained by Nicholson (1976b) and Nicholson et al. (1979) from the mortality experience of a smaller group of miners and millers employed 20 or more years at Thetford Mines, Quebec. In this study, 178 deaths occurred among 544 men who were employed during 1961 in 1 of 4 mining companies. In the ensuing 16 years of follow-up, 26 deaths occurred from asbestosis, 28 (25 on DC) from lung cancer (11.1 expected), and 1 from mesothelioma.

Fiber measurements were made during 1974 in five mines and mills, and data on particle counts from 1948 were supplied by the Canadian Government. From these data, exposure estimates were made for each of the 544 individuals according to their job histories. Fiber exposures for earlier years were estimated by adjusting current measurements by changes in particle counts observed since 1950. The 20-year cumulative exposure for the entire group was estimated to be 1080 f-y/ml.

The mortality experience of the whole group from an earlier follow-up was reported by two exposure categories (Nicholson, 1976b) (see Table 3-21). The difference in lung cancer SMRs in these two exposure groups suggests that K_L = 0.0023 [(333-55)/(1760-560)/100]. However, Canada rates were used to estimate expected deaths and these overestimated mortality. As with the McDonald

TABLE 3-21. EXPECTED AND OBSERVED MORTALITY AMONG 544 QUEBEC ASBESTOS MINE AND MILL EMPLOYEES, 1961-1973

	Average Exposure 560 f-y/ml			Cumulative Exposure 1760 f-y/ml		
Causes of death	Exp.	Obs.[a]	Ratio	Exp.	Obs.[a]	Ratio
All causes of death	68.29	65	0.95	44.56	67	1.50
All cancers	15.45	15	0.97	10.11	18	1.78
Lung	4.52	7	1.55	3.00	13	4.33
Mesothelioma	--	1	--	--	0	--
Gastrointestinal	4.18	3	0.72	2.71	3	1.11
Other cancers	6.75	4	0.59	4.40	2	0.45
Respiratory diseases	4.79	10	2.09	3.02	15	4.24
Pneumonia	2.01	1	0.50	1.27	1	0.78
Asbestosis	--	7	--	--	11	--
Other respiratory	2.79	2	0.72	1.76	3	1.70
All other causes	48.05	40	0.83	31.43	34	1.08

[a] Best estimate cause of death.

et al. (1980) study, K_L will be multiplied by a factor of 1.5 to 0.0034 and then reduced to 0.0030 to convert to DC lung cancer diagnosis. An analysis, adjusted to local rates, using the overall SMR and average group exposure, yields a value of $K_L = 0.0017$. Because there is likely to be greater uncertainty associated with the regression analysis than with the use of average values, we will use the estimate of $K_L = 0.0017$ for this study.

3.9.9 Mining and Milling, Italy (Chrysotile); Rubino et al. (1979)

A final study of chrysotile mining and milling is that of Rubino et al. (1979) of the Balangero Mine and Mill, northwest of Turin. A cohort was established of 952 workers, each with at least 30 calendar days of employment between January 1, 1930 and December 31, 1965, who were alive on January 1, 1946. Ninety-eight percent of the cohort was traced and their mortality experience through 1975 was ascertained. Overall, an exceptionally high mortality was seen compared to that expected; 332 deaths were observed versus 214.4 expected. The excess mortality, however, was largely confined to nonmalignant respiratory diseases, cardiovascular diseases, and accidents. The overall SMR for all malignant neoplasms was 106, with only cancer of the larynx found to be significantly in excess in the whole group. While the overall data were relatively unremarkable, the age standardized rates of lung cancer according to cumulative dust exposure showed a relative risk of 2.29 (2.54 based upon cancer of the lung and pleura) for a high exposure group (376 f-y/ml) compared to a low exposure group (75 f-y/ml) [K_L = 1.29/(376-75) = 0.0043)]. A case-control analysis of lung cancer according to cumulative dust exposure showed a relative risk of 2.61. Adjusting to a relative risk of 1 at zero exposure gives a K_L of 0.089. However, the characterization of the exposures in the study may have created an artificially steeper dose-response relationship than actually exists. Rubino et al. (1979) calculated the person-years at risk in two exposure categories (±100 f-y/ml). A person contributed to the lower category until his exposure exceeded 100 f-y/ml. However, in Section 3.6 it is shown that there is a 5-10 year lag before the risk is manifest from a given exposure. Thus, the transition should be delayed by 5-10 years after achievement of 100 f-y/ml. Deaths and person-years at risk occurring in this delay period should be attributed to the lower exposure category. If lung cancer deaths occurred in the delay period, the dose-response relationship is probably artificially steeper than it should be; if no lung cancer deaths occurred, it is artificially shallower. The overall SMR of those 20 years from onset yields a K_L of 0.00013 [(103.4 - 100)/100/273 f-y/ml]. The uncertainty in the estimate of K_L is enormous. We will use the geometric mean of 0.0043 and 0.00013, 0.00075, to represent K_L.

3.9.10 Insulation Manufacturing, Paterson, NJ (Amosite); Seidman et al. (1979)

The study by Seidman et al. (1979) also can be used for quantitative risk estimates. The study was recently updated and the new mortality results were submitted for the OSHA hearings record on a revised standard for asbestos (Seidman, 1984). In this update, dose-response data, based upon estimates of individual exposures for each cohort number, are available. Data for lung cancer are listed in Table 3-22.

Because no data exist on air concentrations for the Paterson factory, the data in terms of fiber counts were estimated from air concentrations in two other plants manufacturing the same products with the same fiber and machinery. One of these plants, in Tyler, Texas, opened in 1954 and operated until 1971; the other, in Port Allegany, Pennsylvania, opened in 1964 and closed in 1972. As in the Paterson factory, efforts to control dust in these newer plants were

TABLE 3-22. CUMULATIVE OBSERVED AND EXPECTED DEATHS FROM LUNG CANCER 5 TO 40 ELAPSED YEARS SINCE ONSET OF WORK IN AN AMOSITE ASBESTOS FACTORY, 1941-1945, BY ESTIMATED FIBER EXPOSURE
(Seidman, 1984)

Cumulative exposure (f-y/ml)	Number of men	Number of deaths (BE)	Number of deaths (DC)	Expected deaths[a]	SMR (BE)	SMR (DC)
<6.0	177	15	14	5.31	282	264
6.0 - 11.9	109	12	12	2.89	415	415
12.0 - 24.9	139	15	15	3.39	442	442
25.0 - 49.9	123	13	12	2.78	468	432
50.0 - 99.9	104	17	17	2.38	714	714
100.0 - 149.9	57	9	9	1.49	604	604
150.0 - 249.9	58	15	12	1.32	1136	909
250+	53	15	11	0.94	1596	1170
Total	820	111	102	20.51	541	497

Estimated average cumulative exposure: 67.1 f-y/ml.

BE = best estimate of cause of death based on all medical evidence.

DC = Death certificate cause of death.

[a] Expected deaths based on New Jersey white male quinquennial age and calendar year period specific death rates.

Regression equations

SMR = 325 + 2.72(±0.54) x f-y/ml weighted
SMR = 330 + 2.45(±0.37) x f-y/ml unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 4.28 (±1.17) x f-y/ml

limited. One, in fact, was housed in a low Quonset-type building where the confined space exacerbated dust conditions. During 1967, 1970, and 1971, asbestos fiber concentrations in these plants were measured by the U.S. Public Health Service and the results published in the Asbestos Criteria Document of the National Institute for Occupational Safety and Health (1972). These data were supplemented by company data in one plant and individual worker estimates of dustiness (which were used for some jobs not sampled).

The zero dose SMR intercept of 325 is highly anomalous and difficult to understand. The use of New Jersey rates for calculating expected deaths is appropriate for the Paterson area (the age standardized county rates are 46.8 versus 46.3 for the state). The high intercept is largely the result of a disproportionately high risk observed in individuals employed for less then 6 months, whose SMR is 295 (32 observed, 10.86 exposed). Certainly, new employees usually get the dustiest jobs and if there are effects of intensity of exposure separate from those of dose, very dusty environments may have contributed a disproportionately greater risk. However, longer term employees also would have had such jobs at one time and intensity effects are not seen in other asbestos-exposed groups. Another possibility is that the short-term group includes many men exposed to carcinogens at work elsewhere or they are unusually heavy smokers. Abnormally high risks were also seen in the short-term employees of a friction products plant studied by McDonald et al. (1984). A third possibility is that there could have been misestimates of exposure for the short-term employees who would have the extremely dusty jobs. However, the dose-response relationship for death from asbestos is a reasonable one and there is no unusual mesothelioma risk among those employed less than 6 months. Finally, part of the excess may simply be the result of statistical fluctuations.

The values of K_L estimated by different treatments of the data range from 0.0084, obtained by adjusting the slope of the weighted regression line by the intercept (2.72/325), to 0.059, obtained by dividing the excess overall lung cancer SMR by the average group exposure [(495-100)/67.1/100]. If inappropriate underlying rates (because of other exposures) apply only to the short-term group, an adjustment can be made by forcing the dose-response line through the origin. This yields a value of $K_L = 0.043$. Because this is most likely to be the case, this value will be used for K_L.

The uncertainty in the value extends from 0.0084 to 0.074 to account for the statistical variability on the number of deaths and different values of K_L obtained from different analysis procedures.

3.9.11 Insulation Application, United States (Chrysotile and Amosite)

The previously discussed mortality study of Selikoff et al. (1979) can be combined with published information on asbestos exposures measured for members of this cohort to obtain an exposure-risk estimate. The data on insulation workers' exposure were reviewed by Nicholson (1976a) and are summarized in Table 3-23. Using the standard membrane filter technique of the U.S. Public Health Service for counting asbestos fibers (Leidel et al., 1979), three

TABLE 3-23. SUMMARY OF AVERAGE ASBESTOS AIR CONCENTRATION DURING INSULATION WORK[a]
(Selikoff et al., 1979)

Research group	Average fiber concentration, f/ml Light and heavy construction	Marine work
Nicholson (1975)	6.3	
Cooper and Balzer (1973)	2.7	6.6
Ferris et al. (1971)		2.9
Harries (1971)		8.9
Average concentrations of all visible fibers counted with a konimeter and bright-field microscope.		
Murphy et al. (1971)		8.0
Fleischer et al. (1946)		30-40
Estimates of past exposure based on current membrane-filter data.		
Nicholson (1976a)	10-15	

[a] Average concentrations of fibers longer than 5 μm evaluated by membrane filter techniques and phase-contrast microscopy.

Source: Nicholson (1976a).

different laboratories in the United States found that the average fiber concentration of asbestos dust in insulation work, between 1968 and 1971, ranged from about 3 to 6 f/ml. A similar study in the Devonport Naval Dockyard in Great Britain, with the same techniques, obtained 8.9 f/ml for the average of long-term sampling of asbestos concentrations measured during application of insulating materials aboard ship (Harries, 1971). In the research that led to these data, it was reported that peak exposures could be extremely high. It was not uncommon, for example, to get 2- to 5-minute concentrations of asbestos exceeding 100 f/ml during the mixing of cement. This mixing, however, would only be done perhaps once an hour, so that exposures measured during that hour, including the mixing, would seldom average more than 10 f/ml. Similar experiences were subsequently reported by Cooper and Miedema (1973), who stated, "Peak concentrations may be high for brief periods, while time-weighted averages are often deceptively low."

Direct information on asbestos fiber concentration, measured by the currently prescribed analysis procedures, has been available only since 1966. Although insulation materials have changed from earlier years (fiber glass has found extensive use, and work with cork is seldom done today) and changes in the asbestos composition of insulating products have taken place (pipe coverings and insulation blocks may have had twice the asbestos content in earlier years), work practices are virtually identical and few controls of consequence were in use. Therefore, dust concentrations measured under these conditions have relevance for estimating the levels of past years. Considering the possible doubling of the asbestos content of older insulation materials, the data from the studies listed in Table 3-23 suggest that the average exposures of insulation workers in the United States during past years could have ranged from 10-15 f/ml for commercial and industrial construction. In marine construction, it may have been between 15 and 20 f/ml. We will use a value of 15 f/ml as an overall average. Because of the great variability in work activities of this group, the range of uncertainty in the exposure is estimated to be from 7.5 to 45 f/ml, and this range is indicated in Figure 3-7.

This information and the data in Figure 3-4 allow one to calculate a lung cancer risk per unit of asbestos exposure (in f-y/ml) from the linearly rising portion of the curve, the slope of which is 0.16 per year or 0.07 per f-yr/ml (for an exposure intensity of 15 f/ml). However, the data of Figure 3-4 utilized BE (best estimates) in establishing lung cancer mortality. Adjusting to DC (death certificate) diagnosis reduces the value of K_L from 0.011 to 0.0094 (0.011 x 3.06/3.60). The statistical uncertainty on the estimate of risk is very low. However, there is no independent indication that the use of U.S. mortality rates is appropriate. Hammond et al. (1979a) reported that 53.5 percent of insulation workers were current cigarette smokers, 27.3 percent were past smokers, and 17.2 percent never smoked cigarettes. The corresponding data for the 1967 U.S. population were 49.1 percent current smokers, 23.6 percent past smokers, and 27.3 percent non-cigarette smokers (Harris, 1979). This difference would only affect the underlying rates by about 10 percent. However, because insulation workers may have smoked more cigarettes, we will reduce the value of K_L by 20 percent to 0.0075.

3.9.12 Asbestos Products Manufacturing, United States (Chrysotile and Crocidolite); Henderson and Enterline (1979)

The data of Henderson and Enterline (1979) (Figure 3-1 and Table 3-24) can also be used to establish fiber dose-response data even though their data were presented in terms of total dust concentrations measured in millions of particles per cubic foot (mppcf). No data exist on the conversion between mppcf and f/ml for most of the plants studied. However, there are data on the relationship between fiber and total dust concentrations in textile operations and asbestos cement production. Dement et al. (1982) found that conversion of 3 f/ml/mppcf was appropriate to most textile operations, although Ayer et al. (1965) had earlier suggested a value of 6 f/ml/mppcf. In a plant making asbestos cement pipe and sheets, Hammad et al. (1979) determined the conversion value to be 1.4. It would be expected that the cement products value would be most applicable to the Henderson and Enterline circumstance because of the extensive use of cement and other mineral particles (e.g., calcium silicate, talc, SiO_2, MgO) in asbestos products manufacturing. The least squares weighted regression line of SMR on dose is SMR = 143 + 0.51 x mppcf-y (see Table 3-24). Using a value of 1.5 f/ml/mppcf to represent the conversion relationship, the estimate of K_L is 0.0034 (0.51/100/1.5).

TABLE 3-24. LUNG CANCER RISKS, BY DOSE, AMONG RETIREES OF U.S. ASBESTOS PRODUCTS MANUFACTURERS (Henderson and Enterline, 1979)

Exposure in mppcf-y	SMR
62 (<10)	197.9 (19)[a]
182 (10-19)	180.0 (9)
352 (20-39)	327.6 (19)
606 (40-79)	450.0 (9)
976 (>80)	777.8 (7)
Complete cohort:	270.4 (63)

Estimated average cumulative exposure: 249 mppcf-y.

[a] () = number of deaths.

Regression equations

SMR = 143 + 0.51(±0.13) x mppcf-y weighted
SMR = 100 + 0.66(±0.07) x mppcf-y unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 0.64 (±0.097) x mppcf-y

As described previously, observing a cohort beginning at age 65 may seriously understate the full impact of asbestos exposure. Most of the workers in this cohort began employment prior to age 25. To partially account for selection effects among retirees, we will multiply the above value by 1.45. [This adjustment is the ratio of the lifetime mortality from age 25 to lifetime mortality at age 65 (see Table 3-8)]. Thus, K_L is adjusted to a value of 0.0049.

3.9.13 Asbestos Cement Products, United States (Chrysotile and Crocidolite); Weill et al. (1979); Hughes and Weill (1980)

A study of an asbestos cement production facility also provides exposure-response information (Weill et al., 1979; Hughes and Weill, 1980), as shown in Table 3-25. Although the experience of 5645 individuals was reported, 1791 of whom had been employed for longer than two years, the dose-response information is uncertain because of limitations in the mortality data. Of even greater significance, tracing was accomplished through information supplied on vital status by the Social Security Administration, and this information only allowed the vital status of 75 percent of the group to be determined. Those individuals untraced were considered alive in the analyses, which assumption may have led to serious misestimates of mortality because prior to 1970, many deaths, particularly of blacks, were not reported to the Social Security Administration. The percentage of unreported deaths of both sexes ranged from nearly 80 percent in 1950 to 15 percent in 1967 (Aziz and Buckler, 1980). Thus, many cohort members could be deceased, a fact unknown to the researchers. This could likely be the source of the extraordinarily low overall reported mortality of the cohort, which allowed deficits of about 40 percent in several exposure categories. (The overall SMR is 68.)

Two methods of adjustment for incomplete trace can be made. In one, the overall SMR for lung cancer is divided by the SMR for causes other than lung and gastrointestinal cancer (66). This yields a value of $K_L = 0.0064$, using a value of 64 mppcf for the group exposure and a fiber-particle conversion factor of 1.4 (Hammad et al., 1979) [((104/66)-1)/64/1.4]. Alternatively, a regression of SMR on dose yields SMR = 70 + 0.43 x mppcf-y. The low value of SMR is probably the result of missing deaths. If the percent missing is similar in each category then $K_L = 0.0042$ (0.43/100/1.4/0.70). We will use the average of these values, 0.0053, for the point estimate of K_L. The assumption that there is an equal percentage of missing deaths in each category is

TABLE 3-25. LUNG CANCER RISKS, BY DOSE, AMONG ASBESTOS CEMENT PRODUCTION WORKERS (Weill et al., 1979)

Exposure in mppcf-y[a]	SMR	RR[b]
5 (<10)	77 (19)[c]	1.00
25 (11-50)	70 (8)	1.14
75 (51-100)	26 (1)	0.52
150 (101-200)	290 (9)	2.85
400 (>200)	226 (14)	2.75
	104 (51)	

Estimated average cumulative exposure: 63.6 mppcf-y

[a] Accumulated during first 20 years from initial employment.

[b] Relative risk from an internal case-control analysis.

[c] ( ) = number of deaths.

Regression equations

SMR = 70 + 0.43(±0.22) x mppcf-y weighted
SMR = 77 + 0.46(±0.31) x mppcf-y unweighted

RR = .96 + 0.47(±0.18) x mppcf-y weighted
RR = .99 + 0.50(±0.26) x mppcf-y unweighted

Weighted regression equation forced through an SMR of 100:
SMR = 100 + 0.31(±0.22) x mppcf-y

uncertain. There are more untraced in the lowest category but a greater percentage of those untraced in the most exposed group may be deceased. If one considers all of the untraced deaths to be in the lowest exposure categories and forces a regression line through the origin, its slope is 0.0040. These uncertainties in possible methods of adjusting for untraced deaths are indicated in Figure 3-7.

3.9.14 Asbestos Cement Products, Ontario, Canada (Chrysotile and Crocidolite); Finkelstein (1983)

A recent study by Finkelstein (1983) also relates mortality in an asbestos cement products facility to measured exposures. He established a cohort of 241 production and maintenance employees from records of an Ontario asbestos cement factory, consisting of all individuals who had nine or more years of employment beginning prior to 1960. Their mortality experience was followed through October 1980. Impinger particle counts of varying degrees of comprehensiveness were available from various sources (government, insurance company, employer) from 1949 until the 1970s. After 1973, membrane fiber counts were taken. Individual exposure estimates were constructed based on recent fiber concentrations at a particular job. They were modified for earlier years due to changes in dustiness of the job, as determined by the impinger particle counts. These counts were thought to be accurate to within a factor of 3-5. Examples of exposure estimates for the years 1948-1954 for willow operators, forming machine operators, and lathe operators were 40 f/ml, 16 f/ml, and 8 f/ml, respectively.

The lung cancer mortality data are shown in Table 3-26. The dose-response relationship is anomalous. The first two exposure categories show the risk increasing steeply with exposure, but in the last category it falls significantly. Both GI cancer and mesothelioma show a strong positive trend with exposure, suggesting that the exposure rankings are correct. The only regression line that makes sense is one forced through an RR of 1 at zero exposure. This yields a K_L of 0.048, which is close to that calculated from the overall mortality excess and average group exposure. The average cumulative 18-year exposure for the production group in the asbestos cement work was 112.5 f-y/ml. Lung cancer deaths observed in this group were 17 versus 2.0 expected from Ontario rates for an SMR of 850. This yields a value of $K_L = 0.067$ [(850-100)/112.5/100] which will be used as the estimate from this study.

We do not know the reasons for the very significant difference in risk seen in two plants (of the same company) producing the same product. The point estimate of risk from Finkelstein (1983) ($K_L = 0.067$) is 13 times that of Weill et al. (1979) ($K_L = 0.0053$) even after attempting to correct for the incomplete trace of the latter study. Data on the duration of exposure are not given by Finkelstein (1983), but it would appear that the estimated average fiber exposure of his cohort was between 7 f/ml and 12 f/ml. (The average cumulative exposure over 18 years was 112 f-y/ml; all cohort members were employed for at least 9 years, one of which must have been in an asbestos work area.) This average concentration is about half of that estimated by Weill et al. (1979), using the particle-to-fiber conversion of Hammad et al. (1979). It is not possible to evaluate the accuracy of either set of exposure estimates. The exposure estimates of Finkelstein (1983) were submitted to company officials who thought they were reasonable; but worker descriptions of plant

TABLE 3-26. LUNG CANCER RISKS, BY DOSE, AMONG
ONTARIO ASBESTOS CEMENT WORKERS
(Finkelstein, 1983)

Exposure in f-y/ml	Standardized mortality deaths/1000 p-y Lung Cancer
Ontario	1.6
44	13.6 (5)[a]
92	92.1 (7)
180	11.9 (6)
Complete cohort:	850 (17)

Estimated average cumulative exposure: 112 f-y/ml.

[a] () = number of deaths.

Regression equations
(Forced through the value 1.6 at zero exposure)

Lung cancer RR = 1.60 + 0.077 x f-y/ml weighted
Lung cancer RR = 1.60 + 0.108 x f-y/ml unweighted

conditions suggest that very high exposures occurred periodically (Ontario Royal Commission, 1984). In a study of asbestosis in the Ontario plant (Finkelstein, 1982), data comparable to that of Berry et al. (1979) were obtained. Finkelstein observed prevalence rates of asbestosis of 4 percent and 6 percent at 50-99 f-y/ml and 100-149 f-y/ml versus 2.5 percent and 8.5 percent by Berry et al. (1979). Henderson and Enterline (1979) observed SMRs of 231 and 522 among retirees of cement sheet and shingle workers and cement pipe workers, respectively. These values are more consistent with the higher risk of Finkelstein (1983) than the lower one of Weill et al. (1979). In Figure 3-7, a fivefold downward uncertainty is indicated in K_L to reflect the maximum stated uncertainty in the exposure estimates of Finkelstein (1983).

3.9.15 Lung Cancer Risks Estimated in Other Reviews

A number of other individuals or groups have also estimated unit exposure risks for lung cancer from these same epidemiological studies. These are shown in Table 3-27. Because of general agreement on the appropriate model for lung cancer, the unit exposure risks estimated in this document are very

TABLE 3-27. COMPARISON OF ESTIMATED LUNG CANCER RISKS BY VARIOUS GROUPS OR INDIVIDUALS IN STUDIES OF ASBESTOS-EXPOSED WORKERS

Study	Percent increase in lung cancer per f-y/ml of exposure (100 x K_L)						
	This Document	CPSC[a]	NAS[b]	Ontario Royal Commission[c]	Liddell and Hanley (1985) mppcf-y	Liddell and Hanley (1985) f-y/ml	Doll and Peto (1985) f-y/ml
Dement et al. (1983b)	2.8	2.3	5.3	4.2	6.9	2.4	
McDonald et al. (1983a)	2.5				5.9	2.0	1.25
Peto (1980) after 1950	1.1	1.0	0.8	1.0			1.5
before 1951			0.07				0.54[d]
McDonald et al. (1983b)	1.4				5.1	1.7	
Berry and Newhouse (1983)	0.058	0.06		0.058	0.00	0.00	
McDonald et al. (1984)	0.010				0.00	0.00	
McDonald et al. (1980)	0.06	0.06	0.06	0.020-0.046	0.16	0.05	
Nicholson et al. (1979)	0.17	0.12	0.15				
Rubino et al. (1979)	0.075	0.17					
Seidman (1984)	4.3	6.8[e]	9.1[e]		3.3[e]	1.1	
Selikoff et al. (1979)	0.75	1.0	1.7	1.0	3.7	1.2	
Henderson and Enterline (1979)	0.49	0.50	0.3	0.069	0.35	0.23	
Weill et al. (1979)	0.53	0.31			0.66	0.47	
Finkelstein (1983)	6.7	4.8		4.2[f]			
Newhouse and Berry (1979) Males			1.3				
Females			8.4				
Values used for risk extrapolation		0.3-3.0	2.0	0.02-4.2			1.0
Geometric mean of all studies	0.65						
Geometric mean excluding mining and milling	1.0						

[a] U.S. Consumer Product Safety Commission (1983).

[b] National Academy of Sciences (1984).

[c] Ontario Royal Commission (1984).

[d] All men employed after 1932.

[e] Data from Seidman et al. (1979).

[f] Unpublished data supplied to the Commission.

similar to those estimated by others. The differences in the values lie in the choice of the method to obtain a dose-response relationship and the treatment of potential biases in a study.

3.9.16 Summary of Lung Cancer Dose-Response Relationships

The results of all the determinations of K_L, the fractional increases in lung cancer risk per f-y/ml exposure, are displayed in Figure 3-7, along with estimates of statistical variation, adjustments for possible biases, and estimates of uncertainties associated with exposure determinations. The details of the calculations of statistical uncertainty are provided in Table 3-10, which also shows that the confidence limits associated with an individual value of K_L are large. The uncertainties are largely the result of statistical variations associated with small numbers and uncertainties in exposure measurements. However, statistical variabilities appear to be more important. In 9 of the 14 studies, uncertainties in the measure of response contribute more to the overall uncertainties than do uncertainties in the measure of exposure. Three studies have 95 percent confidence limits of about two orders of magnitude.

Figure 3-7 displays the unit exposure risks in 14 studies, by predominant fiber type in the exposure and by industrial process. Table 3-28 lists the geometric mean of the unit exposure risks, estimated for the different industrial processes, showing substantial differences in the risks observed, even between processes using predominantly the same asbestos mineral. Significantly lower unit exposure risks ($p < 0.05$) are associated with chrysotile mining and milling and friction product manufacturing compared to the other three processes studied. However, because of the great uncertainty associated with the unit exposure risks in friction products manufacturing, the level of significance of the difference is less than for mining and milling.

There is reasonable agreement between the unit risks observed in different studies within a given industrial process. In the case of textile production, even though the cohorts studied by Peto (1980) and McDonald et al. (1983b) were exposed to some quantities of crocidolite, the unit risks were very similar to that of the plant studied by Dement et al. (1983b) and McDonald et al. (1983a). The only substantial difference in the four groups exposed to mixed fibers in manufacturing processes is the high unit risk observed in the study of Finkelstein (1983). Whether this is real or the result of uncertainties in the study cannot be established at this time. There is no statistical

TABLE 3-28. WEIGHTED GEOMETRIC MEAN VALUES AND ESTIMATED 95 PERCENT CONFIDENCE LIMITS ON K_L FOR THE VARIOUS ASBESTOS EXPOSURE CIRCUMSTANCES DEPICTED IN TABLE 3-10 AND FIGURE 3-7.

Asbestos process or use	Fiber exposure	Geometric mean value of K_L	95% confidence interval
Textile production	Predominantly Chrysotile	0.020	(0.0096 - 0.042)
Friction products manufacturing	Chrysotile	0.00023	(0.00010 - 0.0051)
Mining and milling	Chrysotile	0.00098	(0.00028 - 0.0034)
Amosite insulation production	Amosite	0.043	(0.0084 - 0.074)
Mixed product manufacturing or use	Amosite Chrysotile Crocidolite	0.0068	(0.0035 - 0.013)
All processes	Amosite Chrysotile Crocidolite	0.0065	(0.0025 - 0.017)
All processes except mining and milling	Amosite Chrysotile Crocidolite	0.010	(0.0040 - 0.027)
Textile production and mixed product manufacturing or use	Amosite Chrysotile Crocidolite	0.013	(0.0074 - 0.024)

difference in the unit exposure risk seen in the group exposed only to amosite asbestos compared to those exposed predominantly to chrysotile in textile production or to mixed fibers in manufacturing.

The origin of the differences in unit exposure risks between mining and milling and other chrysotile exposure circumstances is not completely clear. It was suggested by many individuals, including McDonald et al. (1984), that the differences between mining and milling and various production processes may be related to differences in the fiber size distributions. As in the review of experimental studies (Chapter 4), fiber length and diameter strongly affect the potential for fibers to produce mesothelioma. Corresponding data are not available for lung cancer, but it would be expected that different fiber size distributions would produce different responses. There are many long and curly fibers present in the environment of miners and millers which are easily counted, but not easily inspired because of their large equivalent diameter. In asbestos-using industries, as fibers are broken apart a greater percentage are deposited in the lung. Many of these will remain within a carcinogenic size range. However, the number counted by the membrane filter procedure compared to the number that are potentially carcinogenic may substantially decrease in such circumstances.

As shown in Table 3-28, the geometric mean value of K_L, using data from all studies, is 0.0065, and that for all studies exclusive of mining and milling is 0.010. Because the mining and milling exposures (long and curly fibers, preprocessed) are likely to be less typical of those experienced in the environment (processed, see also Sections 3-8, 3-9, 3-17, 4-2, and 5-1 to 5-8), the best estimate for the fractional increased risk of lung cancer, K_L, for environmental asbestos exposures appears to be 0.010. This value is the same as that used by the Occupational Safety and Health Administration in their risk assessment for the proposed revision to the asbestos standard (OSHA, 1983). OSHA's analysis also was based on risks in studies other than chrysotile mining and milling. The value is one-half that which was adopted by the National Academy of Sciences in their risk analysis (National Academy of Sciences, 1984). The NAS value was based on rounding upward, to 0.02, a median risk of 0.011 estimated in a group of 11 epidemiological studies.

The 95 percent confidence limits on the value 0.010 for K_L are from 0.0040 to 0.027 (a factor of 2.5). This is the result of the analysis of variance in 11 separate estimates. The 95 percent confidence limits on the value of K_L that might be measured in any unstudied exposure circumstance is estimated to be a factor of 10 (8.3 by calculation). The range of uncertainty may, in fact, be greater than the 10 fold factor estimated here, but insufficient information exists by which to make any more precise or definite estimate.

3.10 TIME AND AGE DEPENDENCE OF MESOTHELIOMA

In contrast to lung cancer, for which a relative risk model well explained the data, mesothelioma is best described by an absolute risk model in which the incidence is independent of the age at first exposure and increases according to a power of time from onset of exposure. The rationale for such a model describing human carcinogenesis was discussed by several authors (e.g., Armitage and Doll, 1961; Pike, 1966; Cook et al., 1969). Such a model was utilized by Newhouse and Berry (1976) in predicting mesothelioma mortality among a cohort of factory workers in England. Specifically, they matched the incidence of mesothelioma to the relationship

$$I_M = c(t - w)^k \qquad (3\text{-}4)$$

where I_M is the mesothelioma incidence at time t from onset of exposure, w is a delay in the expression of the risk, and c and k are empirically derived constants. The incidence of asbestos-induced mesothelioma in rats (Berry and Wagner, 1969) followed this time course. In the case of the analysis of Newhouse and Berry (1976), the data suggested that the value of k was between 1.4 and 2 and w between 9 and 11 years. However, the relatively small number of cases available for analysis led to a large uncertainty in the values estimated for either k or w. Peto et al. (1982) recently analyzed mesothelioma incidence in five groups of asbestos-exposed workers. In one study analyzed, that of Selikoff et al. (1979), the number of cases of mesothelioma were sufficiently large that the age dependence of the mesothelioma risk could be investigated. Peto et al. (1982) showed that the absolute incidence of mesothelioma was independent of the age at first exposure and that a function, $I_M = ct^{3.2}$ (see Equation 3-4), fit the data well between 20 and 45 years from onset of exposure. However, observed incidence rates for earlier times were less than those projected, and the authors suggested that an expression proportional to $(t - 10)^2$ better fit the data up to 45 years from onset of exposure. The analysis of Peto et al. (1982) excluded individuals first employed before 1922 and after 1946 and over the age of 80; the fit to the mortality of the entire group suggested a value of k of about 5.

Figure 3-8 shows the risk of death of mesothelioma, according to age, for individuals first exposed between ages 15 and 24 and between ages 25 and 34. As can be seen, these data, although somewhat uncertain because of small numbers, are roughly parallel and separated by 10 years, as was the relative risk for lung cancer. Thus, the absolute risk of death from mesothelioma appears to be directly related to onset of exposure and is independent of the age at which the exposure occurs. The risk of death from mesothelioma among the insulation workers is plotted, according to time from onset of exposure, on the right side of Figure 3-8. It increases to 40 years from onset of exposure. Thereafter, the increase is less. There is even a decrease in the

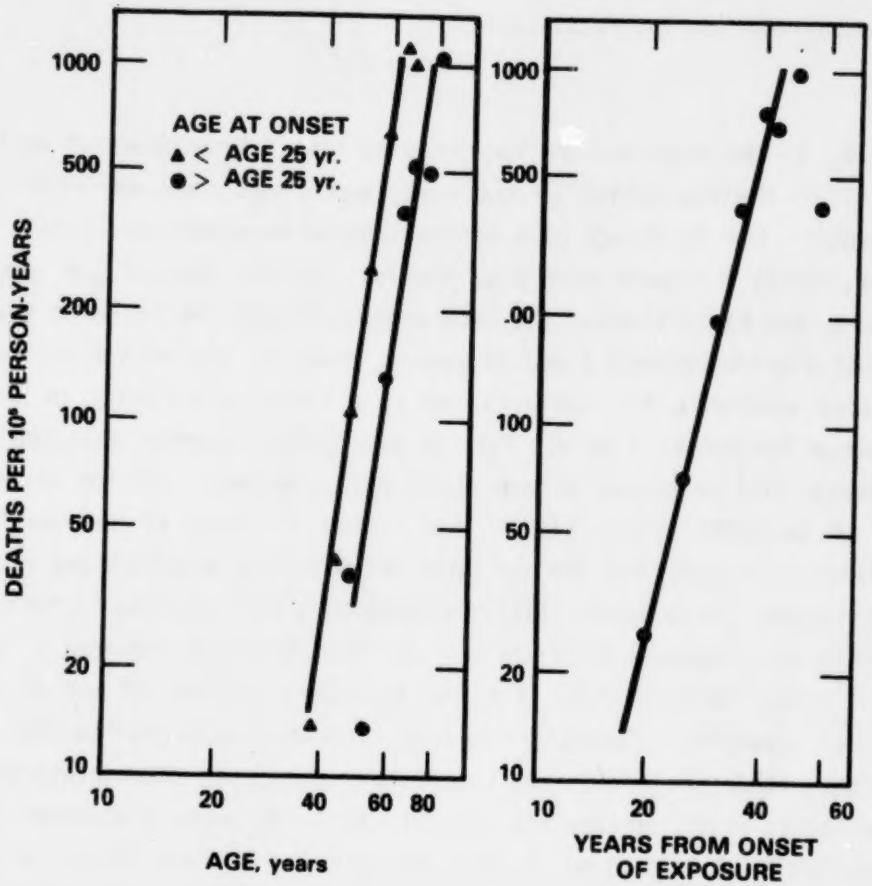

Figure 3-8. The risk of death from mesothelioma among insulation workers according to age and years from onset of exposure. The risk of death according to age is shown separately for insulators first employed before age 25 and after age 25. Data supplied by I.J. Selikoff and H. Seidman.

Source: Nicholson et al. (1982).

risk at 50+ years from onset. This can be the result of misdiagnosis of the disease in individuals age 75 and older, statistical fluctuations associated with small numbers, or selection factors also seen in the risk of lung cancer (e.g., those who lived to age 80 may have had jobs with much lower exposure).

The graph of Figure 3-8 is also represented by an equation of the form

$$I_M = c \cdot f(t-w)^{k+1} \tag{3-5}$$

The data of Figure 3-8, however, are not sufficient to separately specify w and k. If w is 0, k lies between 4 and 5. If w is 10, k lies between 2 and 3. To estimate the risk from long-term exposures; consider an exposure of duration d that began T years ago. The incidence of mesothelioma at time t from the entire exposure is

$$I_M = c \cdot f \cdot \int_{T-d}^{T} (t-10)^k dt \tag{3-6a}$$

assuming a delay of 10 years. The choice of a delay of 10 years is indicated by the data on lung cancer risk, where a delay of from 5 to 10 years was observed between asbestos exposure and the manifestation of risk. f is the intensity of the asbestos exposure, and as used in Equation 3-6, assumes a linear relationship between intensity of exposure and risk (see Figures 3-4 and 3-5). Equation 3-6 is also linear in dose for short duration exposures. Equation 3-6 yields

$$\begin{aligned} I_M &= \frac{c}{k+1} \cdot f \cdot [(t-10)^{k+1}]_{T-d}^{T} \\ &= \frac{c}{k+1} \cdot f \cdot [(T-10)^{k+1}-(T-d-10)^{k+1}] \end{aligned} \tag{3-6b}$$

Using a value of $k = 2$ (which best fits the workers' data) and letting $c/k+1 = K_M$ leads to the following relations for varying times of exposure:

$$I_M(t,d,f) = K_M \cdot f[(T-10)^3 - (T-10-d)^3] \text{ for: } T > 10+d \tag{3-6c}$$

$$= K_M \cdot f(T-10)^3 \text{ for: } 10+d > T > 10 \tag{3-6d}$$

$$= 0 \text{ for: } 10 > T \tag{3-6e}$$

Here I_M is the mesothelioma incidence at t years from onset of exposure to asbestos for duration d at a concentration f. K_M is carcinogenic potency and may depend on fiber type and dimensionality. Note that I_M depends only upon exposure variables and not upon age or calendar year period.

K_M is the measure of the mesothelioma risk per year. In order to calculate the full effect of an asbestos exposure on an exposed population over time, the calculated incidence per year must be summed for each interval from onset of exposure. In such a calculation, it is necessary to take account of the mortality that occurs in the exposed population as it ages. In practice, such calculations, are carried out by 5-year age and onset of exposure intervals.

3.11 QUANTITATIVE DOSE-RESPONSE RELATIONSHIPS FOR MESOTHELIOMA

Four studies provide information on the incidence of mesothelioma (pleural and peritoneal combined) according to time from onset of exposure, and contain data that allow estimates to be made of the duration and intensity of asbestos exposure. These data are given in Table 3-29. Values for K_M, the potency factor for mesothelioma risk, can be estimated using Equations 3-6c, 3-6d, and 3-6e. Other studies reported cases of mesothelioma, but incidence data are lacking or simply not provided. In others, the data were not given because very few mesothelioma deaths were seen. Thus, some studies with missing data could have a lower value of K_M. Note that we are estimating values of K_M from a biased sample of those studies in which K_L was estimated. A measure of the bias can be estimated by comparing the values of K_M and K_L obtained in each analysis with an analysis of the percentage of deaths from mesothelioma compared to excess lung cancer in other studies. The estimate of K_M for each of the four studies was made by calculating a relative mesothelioma incidence using Equation 3-6 and data on duration and intensity of asbestos exposure. The relative incidence curves were then superimposed on the observed incidence data in each study to obtain the value of K_M. These fits are depicted on Figures 3-9 and 3-10. The four studies are described below and summary data are listed in Table 3-30.

TABLE 3-29. MESOTHELIOMA INCIDENCE BY YEARS FROM ONSET OF EXPOSURE, IN FOUR STUDIES

Years from onset of exposure	Incidence (cases/10,000 person-years)	
	Insulation workers Peto et al. (1982)	Textile workers Peto (1980)
15 - 19	1.2 (2,3)[a]	0.0
20 - 24	3.2 (7,6)	5.7 (1,0)
25 - 29	15.4 (18,29)	13.4 (2,0)
30 - 34	28.9 (16,34)	23.9 (2,0)
35 - 39	52.6 (20,26)	39.4 (2,0)
40 - 44	56.9 (6,19)	
45 - 49	108.1 (14,18)	
50+	66.4 (4,14)	
	Amosite factory workers Seidman (1984)	Asbestos cement workers Finkelstein (1983)
15 - 19	0.0	8.5 (1)
20 - 24	7.4 (1,1)	37.7 (4)
25 - 29	26.2 (3,2)	90.9 (5)
30 - 34	50.8 (4,4)	96.2 (1)
35 - 39	18.4 (0,2)	
40 - 44		
45 - 49		
50+		

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[a] (,) = number of pleural and peritoneal deaths, respectively.

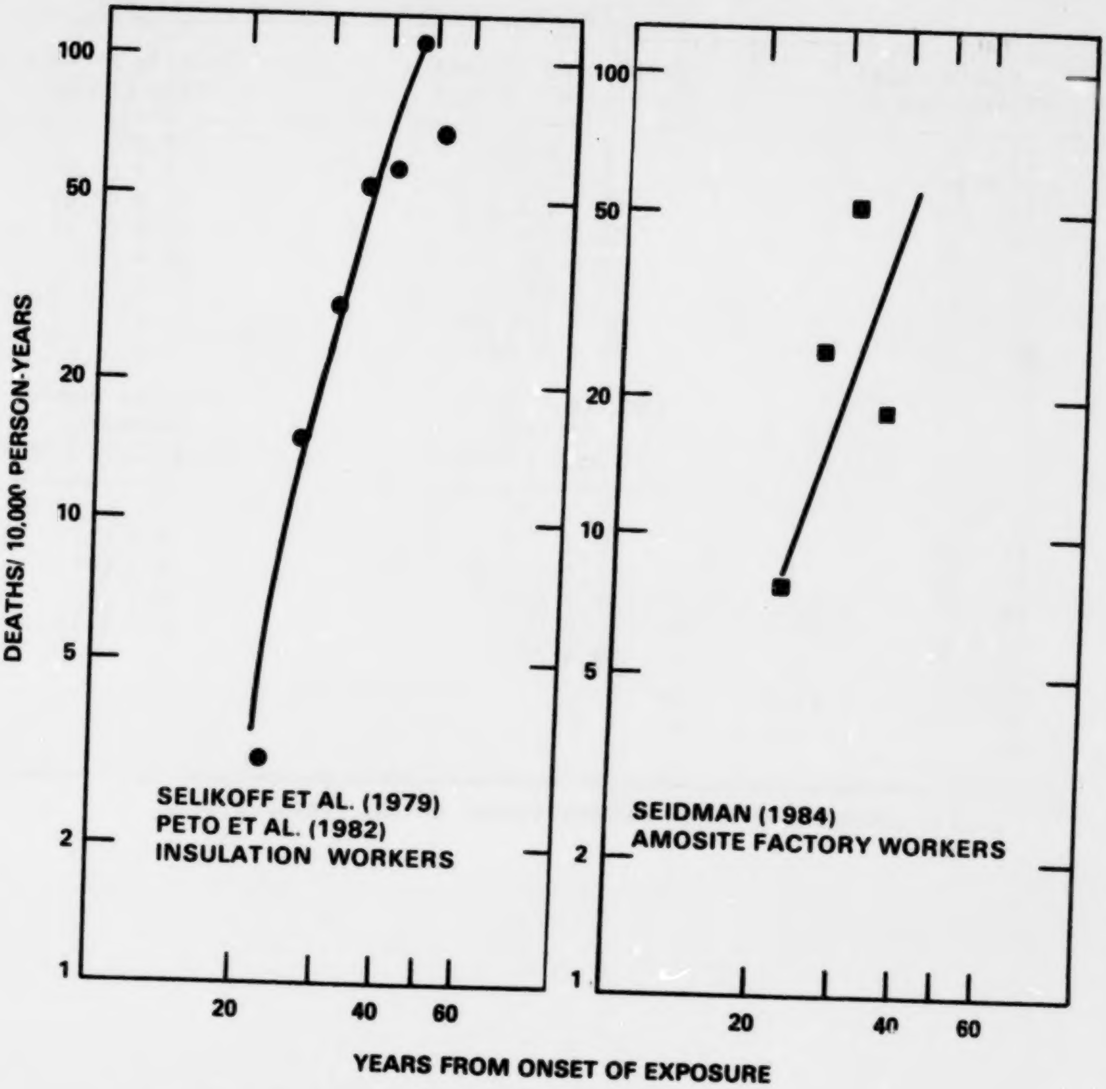

Figure 3-9. The match of curves calculated using Equation 3-6 data on the incidence of mesothelioma in two studies. The fit is achieved for $K_M = 1.5 \times 10^{-8}$ for insulators data and $K_M = 3.2 \times 10^{-8}$ for the amosite workers data.

Source: Peto et al. (1982); Selikoff et al. (1979); Seidman (1984).

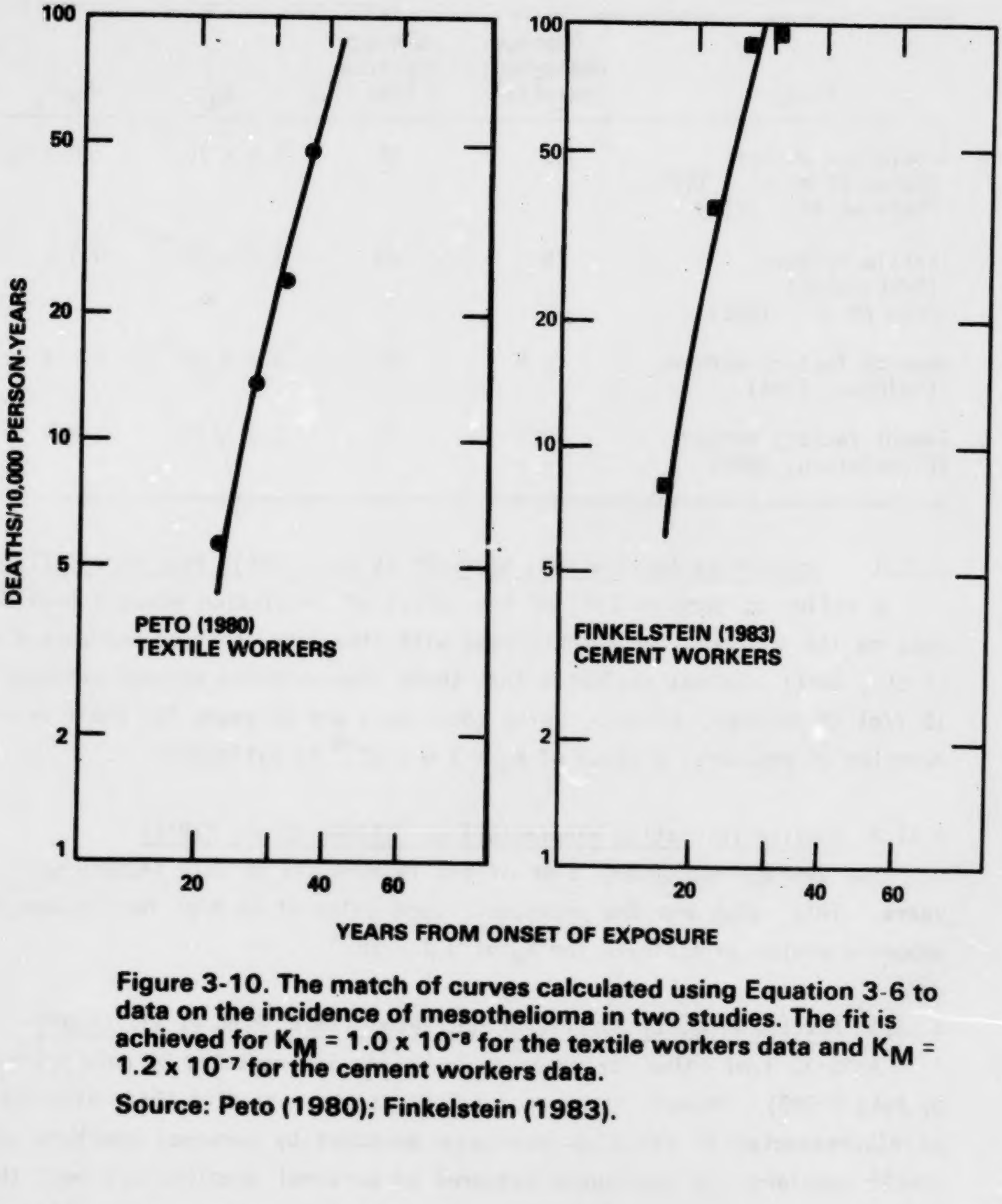

Figure 3-10. The match of curves calculated using Equation 3-6 to data on the incidence of mesothelioma in two studies. The fit is achieved for $K_M = 1.0 \times 10^{-8}$ for the textile workers data and $K_M = 1.2 \times 10^{-7}$ for the cement workers data.

Source: Peto (1980); Finkelstein (1983).

TABLE 3-30. SUMMARY OF THE DATA K_M, THE MEASURE OF MESOTHELIOMA RISK PER FIBER EXPOSURE, IN FOUR STUDIES OF ASBESTOS WORKERS

Study	Average employment duration	Average exposure, f/ml	K_M	K_M/K_L
Insulation workers (Selikoff et al., 1979; Peto et al., 1982)	25	15	1.5×10^{-8}	2.0×10^{-6}
Textile workers (Peto, 1980; Peto et al., 1982)	25	20	1.0×10^{-8}	0.9×10^{-6}
Amosite factory workers (Seidman, 1984)	1.5	35	3.2×10^{-8}	0.7×10^{-6}
Cement factory workers (Finkelstein, 1983)	12	9	1.2×10^{-7}	1.8×10^{-6}

3.11.1 Insulation Application; Selikoff et al. (1979); Peto et al. (1982)

A follow-up through 1979 of the cohort of insulation workers provides data on the incidence of mesothelioma with time from onset of exposure (Peto et al., 1982). It was estimated that their time-weighted average exposure was 15 f/ml (Nicholson, 1976a). Using these data and 25 years for their average duration of exposure, a value of $K_M = 1.5 \times 10^{-8}$ is estimated.

3.11.2 Amosite Insulation Manufacturing; Seidman et al. (1979)

The average employment time of all individuals in this factory was 1.46 years. This value and the previously used value of 46 f/ml for the average exposure yields an estimate for K_M of 3.2×10^{-8}.

3.11.3 Textile Products Manufacturing; Peto (1980); Peto et al. (1982)

A 20-30 f/ml value for exposure intensity is suggested by data presented by Peto (1980). However, some uncertainty exists regarding this value because of discrepancies in relative exposures measured by personal samplers and static samplers. If exposures measured by personal samplers are less than static samplers, as suggested by the data of Smither and Lewinsohn (1973), the average exposure could be about 15 f/ml. Using 20 f/ml and an employment period of 25 years, a value of $K_M = 1.0 \times 10^{-8}$ is estimated.

3.11.4 Asbestos Cement Products, Ontario, Canada; Finkelstein (1983)

The cumulative exposure of the cohort over 18 years was 112 f/yr. Only men with nine or more years of employment were included in the cohort. Although data on the exact duration and intensity of exposure are unavailable, we will use a value of 12 years for duration of exposure and 9 f/ml for the intensity of exposure. This yields a value of $K_M = 1.2 \times 10^{-7}$.

3.11.5 Other Studies

A note on the friction product studies is appropriate. In the study of Berry and Newhouse (1983) little excess lung cancer risk was observed (see Section 3.9.5). Eleven deaths from mesothelioma occurred. A comparison of the work histories of the cases and 40 controls matched for sex, age, and date of hire showed an increased probability of crocidolite exposure among the cases (eight had such exposure) and an increased probability of heavy chrysotile exposure. In the study of McDonald et al. (1984), an elevated risk of lung cancer was observed but no trend with increasing exposures (see Section 3.9.6). McDonald et al. (1984) did not find any mesothelioma deaths among the cohort members. However, three mesothelioma deaths among former plant employees were reported to the Connecticut Tumor Registry (Teta et al., 1983). Two were in women and one in a male who terminated employment prior to receiving a Social Security number and, thus, all were excluded from the cohort of McDonald et al. (1984). Mention of the mesotheliomas is important because it illustrates that cases can occur from chrysotile exposures in friction products manufacture. Because of the low observed lung cancer dose-response relationship in both the studies of McDonald et al. (1984) and Berry and Newhouse (1983), no meaningful data on mesothelioma risk relative to lung cancer can be obtained.

3.11.6 Summary of Mesothelioma Dose-Response Relationships

A review of the four studies for which values of K_M were obtained indicate that three are very similar while K_M from the study of Finkelstein (1983) is much higher. This was also found in the value of K_L estimated in that study. Much closer agreement exists in the ratio of K_M/K_L. While it is not possible to make an accurate estimate of the value of K_M in the 10 other studies used to estimate K_L, a rough measure of mesothelioma risk can be obtained by calculating the ratio of the number of mesothelioma deaths to total deaths and dividing by the cumulative exposures of the groups. This is done in Table 3-31.

TABLE 3-31. ESTIMATE OF A MEASURE OF MESOTHELIOMA RISK RELATIVE TO LUNG CANCER RISK, IN 14 STUDIES

	Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7
Study	Calculated $K_M (\times 10^8)$	K_L	Cumulative exposure (f-y/ml)	$\frac{\text{Mesothelioma deaths}}{\text{Total deaths}}$	$\frac{\text{Col. 4} \times 10^4}{\text{Col. 3}}$	$\frac{\text{Col. 5}}{\text{Col. 2} \times 10^2}$	K_M/K_L
Textile Production							
Dement et al., 1983b		0.028	43.9	0.0041	0.91	0.33	
McDonald et al., 1983a		0.025	30.9	0.0018	0.58	0.23	
Peto, 1980	1.0	0.011	500	0.040	0.80	0.73	0.91×10^{-6}
McDonald et al., 1983b		0.014	50.7	0.016	3.16	2.25	
Friction Products							
Berry & Newhouse, 1983		0.00058	37.1	0.0060	1.62	27.9	
McDonald et al., 1984		0.00010	30.9	0.0030[a]	0.97	97	
Mining and Milling							
McDonald et al., 1980		0.00060	555	0.0030	0.05	0.83	
Nicholson et al., 1979		0.0017	1070	0.0056	0.05	0.29	
Rubino et al., 1979		0.00081	258	0.0045	0.17	2.10	
Amosite Insulation Manufacturing							
Seidman, 1984	3.2	0.043	67.1	0.029	4.26	0.99	0.74×10^{-6}
Insulation Application							
Selikoff et al., 1979	1.5	0.0075	375	0.087	2.32	3.09	2.0×10^{-6}
Asbestos Products Manufacturing							
Henderson & Enterline, 1979		0.0049	373	0.0064	0.17	0.35	
Weill et al., 1979; Weill, 1984		0.0053	89	0.0046[b]	0.652	0.98	
Finkelstein, 1983	12	0.048	112	0.153	13.66	2.85	1.8×10^{-6}
				Geometric means			
				excluding friction products	0.87		
				excluding friction products and studies of Dement and Nicholson	1.07		

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[a] No mesotheliomas were reported in the male cohort studied. However, three mesotheliomas (two in women) were reported from the workforce of the plant studied (Teta et al., 1983). The rough mesothelioma risk calculation uses these three cases and a value of 1000 for the total mortality in the plant work force.

[b] In 1984 testimony before OSHA, Weill reported 9 mesotheliomas among 1953 deaths in his cohort of cement workers.

Column 5 of Table 3-31 indicates this rough mesothelioma risk in all 14 studies, and Column 6 shows the ratio of this risk to 100 x K_L. Note that the two measures of risk are not commensurate. To make this explicit the ratio will be designated as the "relative mesothelioma hazard." The geometric mean of the relative mesothelioma hazard in all studies except friction products manufacturing is 0.87. The ratios in the two friction products studies are very uncertain because of the great uncertainties in the lung cancer risks, and they are not included in the average. Table 3-32 lists the geometric means, by process, of the relative mesothelioma hazards in all studies except Dement et al. (1983b) and Nicholson et al. (1979) (whose mesothelioma cases are included in the larger studies of McDonald et al., 1980, 1983a,b).

The geometric means of the relative mesothelioma hazards, by process, differ very little (excluding consideration of friction products because of the large uncertainties in lung cancer risk.) Textile production, including studies of plants that used some crocidolite and amosite have the lowest average hazard. Product manufacture and use has the highest relative mesothelioma hazard. This is largely the result of the high hazard found among insulation workmen who were exposed only to amosite and chrysotile, but where a review was made of all available pathological material to identify cases. The geometric average of the manufacturing plant studies is 0.99, coincidentally the same as found in amosite insulation manufacture. Chrysotile mining also demonstrated a high relative mesothelioma hazard (although in absolute terms the unit exposure risks for both mesothelioma and lung cancer are lower than other asbestos exposure circumstances). The high relative hazard was, in part, the result of a high relative hazard found in the study of Rubino. Nevertheless, the hazard found in the large study of McDonald et al. (1980), 0.83, is higher than that of textile production (predominantly chrysotile but with some crocidolite and amosite) and little different from all product manufacturing, 0.99, using all types of asbestos. Thus the geometric mean of all studies, 1.07, fairly represents all exposure circumstances, except perhaps, insulation work.

There is no evidence in those studies listed in Table 3-31 and 3-32 that would suggest a substantially different relative mesothelioma hazard for the different types of asbestos varieties. However, this conclusion is limited by the fact that crocidolite was not the dominant fiber exposure in any of the study groups. In an analysis of the risk of pleural and peritoneal mesothelioma relative to excess lung cancer in all published cohorts, including those

TABLE 3-32. ESTIMATED GEOMETRIC MEAN VALUES OF THE RELATIVE MESOTHELIOMA HAZARD (COL. 6 OF TABLE 3-31) FOR THE VARIOUS ASBESTOS EXPOSURE CIRCUMSTANCES LISTED IN TABLE 3-31

	Geometric mean value of relative hazard (Col 6, Table 3-31)
Textiles (except Dement et al., 1983b)[a]	0.72
Friction products	52[b]
Mining and milling (except Nicholson et al., 1979)[a]	1.32
Amosite manufacturing	0.99
Asbestos product manufacturing and use (crocidolite 0% of insulation, 15% of two factories; 5% of Manville plant)	1.32[c]
Geometric mean of all except friction products (excluding Dement et al., 1983b, and Nicholson et al., 1979)	1.07
Geometric mean of all except friction products and mining and milling	1.02

[a] A single mesothelioma case is included in the larger study of McDonald et al.

[b] An unreasonably high value because of low lung cancer risk.

[c] Crocidolite contribution very small and can't extract out relative contribution of crocidolite.

with only crocidolite exposures, it would appear that the ratio of the cases of pleural mesothelioma to excess lung cancers is two to three times greater than that from amosite, chrysotile or mixed fiber exposures. (See Section 3-17, Relative Carcinogenicity of Different Asbestos Varieties.) Considering both pleural and peritoneal sites this ratio increases to three or four times for pure crocidolite exposures. There are no estimates of the relative exposures to crocidolite in those cohorts where such exposure was possible. However, to estimate the possible effect, the relative mesothelioma hazard for the studies of Peto (1980) and McDonald et al. (1983b) were reduced by 20 percent to account for effects of a 2 percent crocidolite usage and those of asbestos products manufacturing by 50 percent. This yields a geometric mean of 0.85 rather than 1.07. This 26 percent difference for an assumed effect of crocidolite in five studies is far less than the tenfold uncertainty in the estimated values of K_L or K_M for an unstudied exposure circumstance. Because of the absence of any evident effect of crocidolite in the values of relative mesothelioma risk in the Table 3-32 and small estimated crocidolite correction to the relative mesothelioma hazard, no adjustment will be made to the final estimated value of K_M (which have associated with it a twentyfold uncertainty in estimating an unknown exposure risk).

The relative mesothelioma hazard in the four studies for which the geometric mean of K_M was calculated is 1.59. The geometric mean of the relative mesothelioma hazard in all studies (excluding friction products) is 1.07. This suggests that the value of K_M/K_L in the four studies is 49 percent higher than the average for all studies. As the geometric mean of the calculated values of K_M/K_L in the four studies is 1.25×10^{-6}, the above data suggest a value of K_M/K_L for all studies of 0.84×10^{-6}. However, this is certainly a lower limit on the value of the ratio. Firstly, inclusion of the friction products studies would raise it by some (unknown) amount. Secondly, 3 of the 4 studies for which K_M/K_L was calculated used data from all available pathological materials and medical records to identify mesothelioma cases, while those not analyzed generally did not. Had all studies done so, the relative mesothelioma hazard would be higher (in the Seidman, 1984 and Selikoff et al., 1979 studies such review increased the number of mesothelioma cases by 75 percent). To partially account for these factors we will use a value of 1.0×10^{-6} for the ratio of K_M/K_L. The average value of K_M is thus 1.0×10^{-8}.

The 95 percent confidence limits on the estimated value of K_L was a factor of 2.5 and a factor of 10 on its application to any unknown exposure circumstance. Larger uncertainty factors would apply to K_M because the data from which it was estimated are more uncertain than those from which K_L was estimated. While it is not possible to estimate the 95 percent confidence limit directly, a factor of 5 would appear to be reasonable for the average value of K_M and a factor of 20 on its application to any unknown exposure circumstance.

The range of uncertainty may in fact be greater than that suggested. While this 20-fold factor provides a range of 400 (i.e., estimates are divided by 20 and multiplied by 20 to determine the range), the range could be greater yet. However, insufficient information exists by which to make any more precise or definite estimate of uncertainty.

3.12 ASBESTOS CANCERS AT EXTRATHORACIC SITES

The consistency of an increased cancer risk and its magnitude, either in absolute (observed-expected deaths) or relative (observed/expected deaths) terms is less for cancer at other sites. Nevertheless, many studies document significant cancer risks at various gastrointestinal (GI) sites. Cancer of the kidney and urinary organs was also found to be significantly elevated in two large studies (Selikoff et al., 1979; Puntoni et al., 1979). Among female workers, ovarian cancer was found in excess (Newhouse et al., 1972; Wignall and Fox, 1982; Acheson et al., 1982). While no other specific sites were shown to be elevated at the 0.05 level of significance, the category of all cancers other than the lung, GI tract, or mesothelioma is significantly elevated (e.g., Selikoff et al., 1979).

Table 3-33 lists all studies in which more than 10 GI cancers were expected or observed and in which the overall lung cancer risk was elevated at the 0.05 level of significance. Some studies having statistically uncertain data were eliminated from consideration, as were several larger studies demonstrating a low risk of lung cancer because of exposure or follow-up circumstances. Because the excess risk of GI cancer is less than that of lung cancer, significantly elevated risks are unlikely to be seen in studies that demonstrate little risk of lung cancer; therefore, negative data in such studies do not have much significance. In considering Table 3-33, note that all but 3 of the 23 listed studies show an excess GI cancer risk, even though the risk is small in several studies. However, 10 of the 23 studies demonstrate risk at a 0.05 level of significance. Figure 3-11 displays the relationship between the relative risk of lung cancer and relative risk of GI cancer in the 23 studies in Table 3-33. Figure 3-11 shows there is a consistent relationship between increased GI cancer risk and increased lung cancer risk. Fiber exposure to the GI tract is probable because the majority of fibers inhaled are brought up from the respiratory tract and swallowed (Morgan et al., 1975), and some may become entrapped within the gut wall (Storeygard and Brown, 1977). Additionally, fibers may be swallowed directly. Nevertheless, the magnitude

TABLE 3-33. OBSERVED AND EXPECTED DEATHS FROM VARIOUS CAUSES IN SELECTED MORTALITY STUDIES

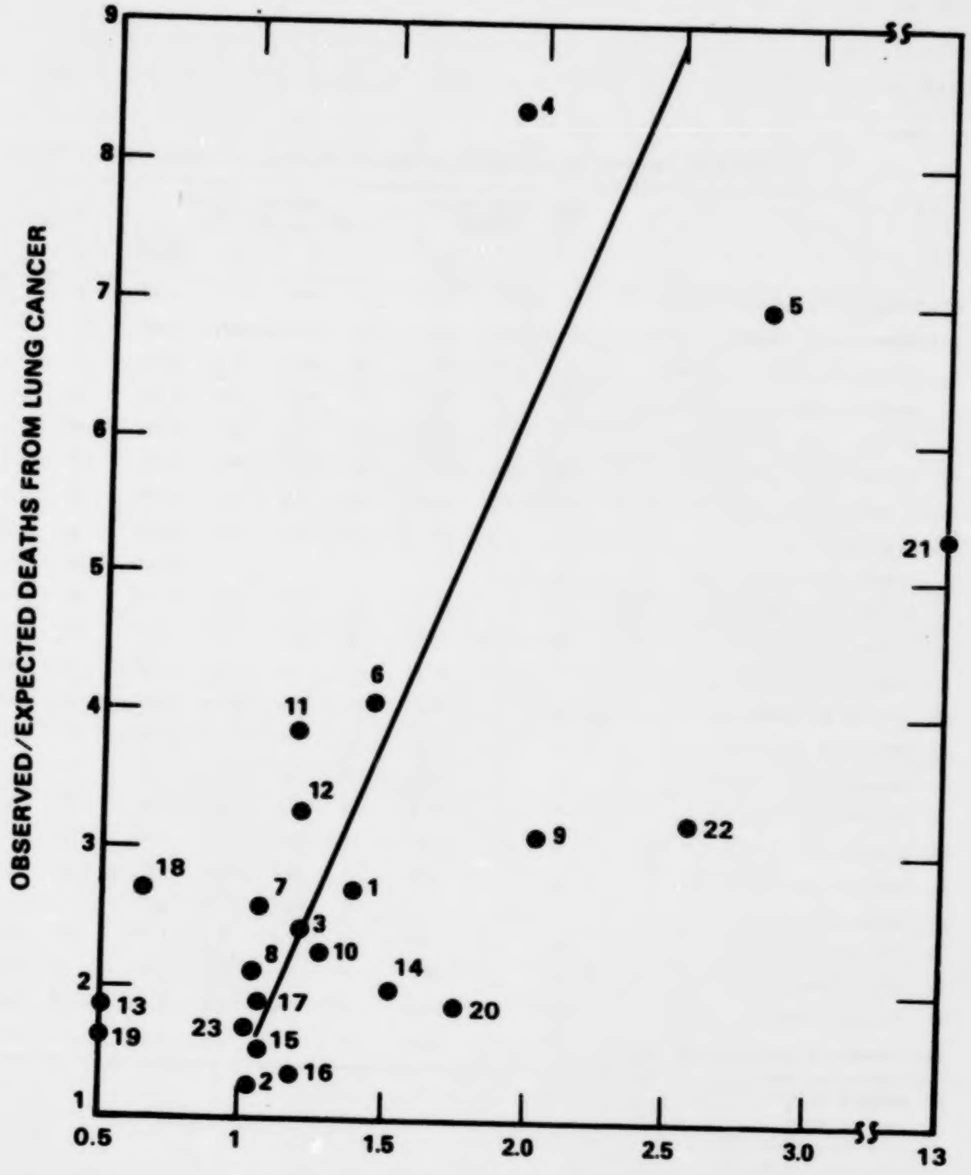
		Respiratory cancer ICD 162-164			Digestive cancer ICD 150-159				Other cancers ICD except 150-59, 162-4, meso			
		O	E	O-E	O	E	O-E	$\frac{(O-E)^d}{(O-E)^r}$	O	E	O-E	$\frac{(O-E)^o}{(O-E)^r}$
1.	Henderson and Enterline (1979)	63	23.3	39.7	55	39.9	15.1	0.380	55	45.6	9.4	0.237
2.	McDonald et al. (1980)	230	184.0	46.0	276	272.4	3.6	0.078	237	217.4	19.6	0.426
3.	Newhouse and Berry (1979) (male)	103	43.2	59.8	40	34.0	6.0	0.100	38	27.4	10.6	0.177
4.	Newhouse and Berry (1979) (female)	27	3.2	23.8	20	10.2	9.8	0.412	33	20.4	12.6	0.529
5.	Selikoff et al. (1979) (NY-NJ)	93[a]	13.1	79.9	43[a]	14.8	28.2	0.353	28[a]	24.5	3.5	0.044
6.	Selikoff et al. (1979) (U.S.)	390	93.7	296.3	89	53.2	35.8	0.121	184	131.8	52.2	0.176
7.	Nicholson et al. (1979)	25	11.1	13.9	10	9.5	0.5	0.036	14	16.1	(2.1)	def.
8.	Peto (1977)	51	23.8	17.2	16	15.7	0.3	0.019	18	24.8	(6.8)	def.
9.	Mancuso and El-attar (1967)	30	9.8	20.2	15	7.1	7.9	0.527	20	6.8	13.2	0.653
10.	Puntoni et al. (1979)	123	54.9	68.1	94	76.6	17.4	0.255	88	81.3	6.7	0.098
11.	Seidman et al. (1979)	83	21.9	61.1	28	22.7	5.3	0.087	39	35.9	3.1	0.037
12.	Dement et al. (1983b)	33	9.8	23.2	10	8.1	1.9	0.082	11	14.1	(3.1)	def.
13.	Jones et al. (1980)	12	6.3	5.7	10	20.3	(10.3)	def.	35	39.5	(4.5)	def.
14.	McDonald et al. (1983a)	59	29.6	29.4	26	17.1	8.9	0.302	35	27.7	7.4	0.252
15.	McDonald et al. (1984)[b]	73	49.1	23.9	59	51.6	7.4	0.309	70	60.4	9.6	0.402
16.	Robinson et al. (1979)	49	36.1	12.9	50	41.4	8.6	0.667	69	51.2	17.8	0.380
17.	Acheson et al. (1984)	57	29.1	27.9	19	17.1	1.9	0.068	33	28.2	4.8	0.172
18.	Wignall & Fox (1982)	10	3.7	6.3	7	10.7	(3.7)	def.	35	21.6	13.4	2.127
19.	Meurman et al. (1974)	21	12.6	8.4	7	14.9	(7.9)	def.		no data		
20.	Albin et al. (1984)	12	6.6	5.4	19	10.8	8.2	1.519	21	20.4	0.6	0.111
21.	Elmes & Simpson (1977)	24	5	19	13	1	12	0.632	10	no data		
22.	Nicholson (1976a)	27[a]	8.4	18.6	13[a]	5.0	8.0	0.430	17[a]	14.4	2.6	0.140
23.	Clemmesen & Hjalgrim-Jensen (1981)	44	27.3	16.7	31	29.9	1.1	0.066	89	93.9	(4.9)	def.

O = observed deaths.
E = expected deaths.
d = digestive cancer.
r = respiratory cancer.
o = other cancer.
ICD = International Classification of Diseases.

def. = no ratio when deficient in O-E.

[a] Best estimate data on causes of death.

[b] Excess risk may not be asbestos-related; see Section 3.9.6.



OBSERVED/EXPECTED DEATHS
FROM GASTROINTESTINAL CANCER

Figure 3-11. The ratio of observed to expected mortality from lung cancer versus the ratio of observed to expected mortality from gastrointestinal cancer.

Source: Table 3-33, reference numbers 1 through 23.

of the excess at GI sites is much less than for the lung. In recent studies, the GI excess is about 10-30 percent of the lung excess.

The number of studies demonstrating a statistically significant excess risk of gastrointestinal cancer in asbestos-exposed groups and the correlation of the relative risk of gastrointestinal with the relative risk of lung cancer are highly suggestive of a causal relationship between asbestos exposure and gastrointestinal cancer. However, alternative interpretations of the above data are possible. Doll and Peto (1985) have suggested that many of the excess cancers attributed to gastrointestinal sites may be misdiagnosed lung cancers or mesotheliomas. They also cite the absence of confirmatory animal data showing a risk of cancer at extrapulmonary sites as weighing against a causal relationship. However, it is difficult to accept that all excess gastrointestinal cancers are the result of misdiagnosis. While cancers of some of the gastrointestinal sites, particularly the pancreas and the stomach to some extent, are often misdiagnosed mesotheliomas, cancers of the colon and rectum are usually correctly certified and the excesses at these sites across studies are unlikely to be the result of misdiagnosis.

The U.S. Environmental Protection Agency Cancer Assessment Group has reviewed studies with GI cancer excess. They have concluded that the association between GI cancer excess and asbestos exposure is strong.

Table 3-33 also lists the observed and expected mortality for cancers other than mesothelioma, the GI, or respiratory tract. The elevation is not as consistent as for GI cancer. Only six studies have elevated risks that are significant at a 0.05 level, and deficits are observed in five. The analysis is further complicated by the possibility that misattribution of lung cancer or mesothelioma may have occurred for some cases. For example, brain or liver cancers could be metastatic lung cancers in which the primary site was not properly identified. In the study of insulation workers, Selikoff et al. (1979) found that 26 of 49 pancreatic cancers were misclassified; most of those misclassified were peritoneal mesotheliomas. The excess at other sites is much less than lung cancer and roughly similar to that of GI cancer.

3.13 ASBESTOSIS

Asbestosis, a long-term disease entity resulting from the inhalation of asbestos fibers, is a chronic, progressive pneumoconiosis. It is characterized by fibrosis of the lung parenchyma, usually radiologically evident only after ten years from first exposure, although changes can occur earlier following more severe exposures. Shortness of breath is the primary symptom, cough is less common, and signs such as rales, finger clubbing, and weight loss in later stages of the disease appear in a proportion of cases. The disease was first reported eight decades ago (Murray, 1907) and has occurred frequently among workers occupationally exposed to the fiber in ensuing years. Characteristic X-ray changes are small irregular opacities, usually in the lower and middle lung fields, often accompanied by evidence of pleural fibrosis or thickening, and/or pleural calcification. Both the visceral and, more commonly, the parietal pleura may be involved.

Currently, 50-80 percent of individuals in groups with heavy occupational exposures beginning more than 20 years earlier are found to have abnormal X-rays. These include asbestos insulation workers (Selikoff et al., 1965), miners and millers (Nicholson, 1976b), and asbestos factory employees (Lewinsohn, 1972). In many circumstances, fibrosis progresses following cessation of exposure. The prevalence of abnormal X-rays is much less in groups exposed to lesser quantities of asbestos, such as shipyard or construction workers or workers exposed recently. Berry et al. (1979) have analyzed the development of clinical and x-ray signs of asbestosis according to accumulated exposure among workers of the Rochdale factory studied by Doll and Peto and others (see Section 3.9.3). The results suggest that the risk of developing possible asbestosis is less than 1 percent from an exposure to 0.7 f/ml for forty years. However, these results must be interpreted cautiously because all individuals studied began work with asbestos after 1950. The possibility of an increasing prevalence of abnormalities with progression of time, even with no further exposure, must be considered.

The British Occupational Hygiene Society (1983) evaluated the clinical, physiological, and X-ray findings among groups of workers exposed in two factories in Great Britain. From an analysis of the data they conclude that the probability of developing any one of seven pulmonary or radiographic abnormalities associated with asbestos exposure is less than 2 percent at cumulative exposures of 25 f-y/ml. As with Berry's analysis, the progression of abnormalities with time must be considered. Findings of abnormal X-rays, predominantly of the pleura, among family contacts of asbestos workers (Anderson and Selikoff, 1979) suggest that radiographic stigmata of asbestos exposure may occur at very low exposures if a long enough time elapses between the exposure and the observation. The significance of pleural X-ray abnormalities is uncertain. They may or may not be associated with deficits in pulmonary function, and no information exists on whether the presence of pleural plaques or pleural thickening implies a greater risk of cancer separate from that associated with cumulative asbestos exposure.

Liddell and McDonald (1980) have correlated cause-specific mortality, 1951-1975, with the readings of the last available employment X-ray of a group of Canadian miners and millers. They found that significantly increased risks of death from pneumoconiosis, pulmonary TB, lung cancer, "other" respiratory disease, and diseases of the heart were associated with a previous abnormal X-ray. However, increased lung cancer risks were also found among individuals with no detected parenchymal fibrosis, but who may have had pleural abnormalities. Again, unknown progression of fibrosis could have occurred between the last reading and death.

In addition to disease and disablement during life, asbestosis has accounted for a large proportion of deaths among workers in some occupational groups. The first reports of the disease (Auribault, 1906; Murray, 1907) described complete eradication of workers in textile carding rooms. Much improvement in dust control has taken place in the industry since the turn of the century, but even recently those exposed to extremely dusty environments, such as textile mills, may have as much as 40 percent of their deaths attributable to this cause (Nicholson, 1976a). Groups with lesser exposures for 20 or more years, such as in mining and milling (Nicholson, 1976b) or insulation work (Selikoff et al., 1979) may have 5 to 20 percent of their deaths attributed to pneumoconiosis. All varieties of asbestos appear equally capable of producing asbestosis (Irwig et al., 1979). In groups exposed at lower concentrations, such as the families of workers, death from asbestosis has not been reported.

It is not clear what the dose-response relationship is for the most minimal manifestations of asbestos exposure, such as a pleural or diaphragmatic plaque or unilateral pleural thickening. The possibility exists that such abnormalities may develop in some individuals long after exposure to very low doses of asbestos (1-10 f-y/ml, for example.) This is suggested by the finding of significant percentages of such abnormalities among family contacts of asbestos workers. However, these x-ray abnormalities are unlikely to be associated with any discernible pulmonary function deficit in individuals exposed to less than 10 f-y/ml. At such exposures, the primary risk consideration is cancer rather than non-malignant disease.

3.14 MANIFESTATIONS OF OTHER OCCUPATIONAL EXPOSURES TO ASBESTOS

In the past decade, considerable evidence was developed on the prevalence of asbestos disease in workers exposed to a variety of work activities. Workers in shipyard trades (other than insulation work), in particular, were shown to have had significant exposure. By 1975, Harries (1976) identified 55 mesotheliomas in the Devonport Dockyard, only two of which were in asbestos workers. In a case-control study of four Atlantic Coast areas, an average relative risk for lung cancer of 1.4 was determined (Blot et al., 1978). The study population had an average employment time of only three years and no exposure data are available. X-ray abnormalities among non-insulator shipyard employees are also common. Among long-term (mostly 30+ year) shipyard workers, 86 percent have X-ray abnormalities characteristic of asbestos exposure (Selikoff et al., 1980). Maintenance personnel are also at risk from asbestos disease. Lilis et al. (1979) reported finding X-ray abnormalities among 55 percent of 20+ year chemical plant workers.

These findings are important because they point to sources of environmental asbestos emissions in the future. Removal of asbestos from friable products, including insulation material, and installation of engineering controls in factories have significantly reduced exposure and emissions from primary manufacturing or new construction work. However, more than one million tons of asbestos are in place as friable materials in ships, buildings, power plants, chemical plants, refineries, and other locations of high temperature equipment (Nicholson, 1976a). Maintenance, repair, and removal of this material will continue to be an important source of future exposure to workers and of emissions into the environment (both inside and outside buildings).

3.15 DEPOSITION AND CLEARANCE

Considerable data are available on the quantity of asbestos fibers in lungs of individuals with and without known exposures to asbestos (Sebastien et al., 1979; Jones et al., 1980; Wagner et al., 1982). Most of the cases analyzed were selected because of death from mesothelioma, often coupled with an investigation of a specific work group (Wagner et al., 1982; Berry and Newhouse, 1983). However, they have not been correlated with known cumulative exposures. Generally, amphibole burdens of heavily exposed individuals range from 10^7 to 10^8 fibers/gram dry weight; general population controls (in Great

Britain) are usually less than 10^6 fibers/gram dry weight (Jones et al., 1980). Similar concentrations of chrysotile are seen in exposed workers (Wagner et al., 1982) and unexposed controls (Jones et al., 1980).

Very few data are available that provide a basis for establishing a model for the deposition and clearance of fibers in humans. It is expected that both short- and long-term clearance mechanisms exist in humans, as in animals (see Chapter 4). If only long-term processes are considered (characterized by months or years) the simplest model is one in which the change in lung burden (N) is proportional to the rate of deposition of fibers (A) (assuming continuous exposure) diminished by a clearance that is proportional (by factor β) to the number of fibers present.

$$\frac{dN}{dt} = A - \beta N \qquad (3\text{-}7a)$$

This yields for the number of fibers present after a constant exposure of duration, t_1,

$$N = \frac{A}{\beta}(1-e^{-\beta t_1}) \qquad (3\text{-}7b)$$

and at a time, t_2 after cessation of a constant exposure of duration t_1

$$N = \frac{A}{\beta}(1-e^{-\beta t_1})e^{-\beta t_2} \qquad (3\text{-}7c)$$

Such a model is applicable at times t_1 and t_2 which are long compared to any short-term clearance mechanisms. It is clearly a very simplistic model in that it considers only one characteristic time for long-term removal processes. Nevertheless, it illustrates the difficulty of applying even the simplest model. In order to systematize lung burdens, information is needed on the duration and intensity of the exposure and the time from last exposure in order to obtain a measure of the characteristic removal time for a given fiber type. Such information is not yet available for the individuals whose lungs have been analyzed.

Data have been presented by Bignon et al. (1978) on the number of amphibole fibers detected in lung washings of seven asbestos insulation workers. All were exposed between 10 and 16 years. While individual exposures are unknown, fewer fibers were found in the washings of those longest removed from exposure. The data are consistent with a decrease of 50 percent in the number of washable fibers at five to seven years after cessation of exposure. However, it is noted that washable fibers may not be proportional to the residual lung burden or to the number of fibers trapped within lung tissue. The lung washings were largely amphibole; no corresponding data are available for chrysotile fibers.

Data on the fiber dimensions from these studies show a decrease in the average length and diameter of fibers found in the pleura compared with those found in the parenchyma. However, no distinction was made between amphiboles and chrysotile in this analysis, and the different length-width data could simply be a reflection of the predominance of chrysotile in the pleura.

3.15.1 Models of Deposition and Clearance

The Task Group on Lung Dynamics of the International Commission on Radiological Protection proposed a model for the deposition and retention of particles (see Brain and Valberg, 1974). The results of this model are shown in Figure 3-12, which depicts the percentages of particles of different sizes deposited in the various compartments of the respiratory tract. Figure 3-12 shows that alveolar deposition is dominant for particles with a mass median diameter less than 0.1 µm. As the particle size increases, deposition in this area decreases, falling to 25 percent at 1 µm and to 0 at 10 µm or above. Nasal and pharyngeal surface deposition becomes important above 1 µm and rises rapidly to be the dominant deposition site for particles 10 µm in diameter or greater. This model was developed for spherical particles. Timbrell (1965) has shown that the settling velocities of particles, and their aerodynamics, are such that fibers with aspect ratios greater than three behave like particles with a diameter three times as great, independent of the length of the fiber. This was corroborated by calculations of Harris and Fraser (1976). Thus, few fibers with diameters as large as 2 µm are likely to penetrate into the alveolar spaces, although finer fibers, even as long as 200 µm, may do so.

3.16 EFFECTS OF INTERMITTENT VERSUS CONTINUOUS EXPOSURES

Two distinct kinds of exposure occurred to workers in the different studies reviewed. In some production operations (e.g., textiles), workers are

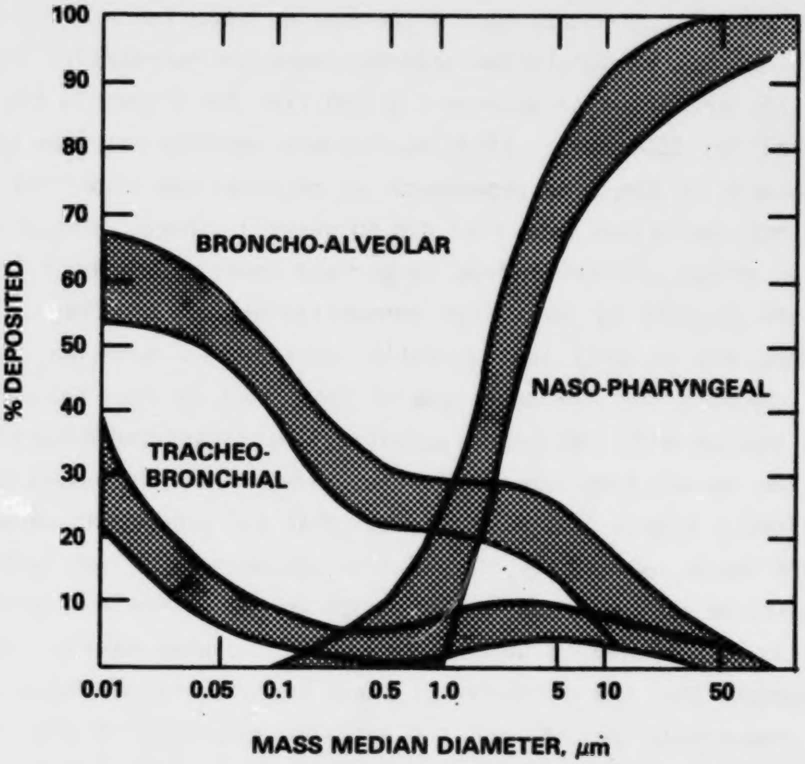


Figure 3-12. Aerosol deposition in the respiratory tract. Tidal volume is 1,450 ml; frequency, 15 breaths per minute. Variability introduced by change of sigma, geometric standard deviation, from 1.2 to 4.5. Particle size equals diameter of mass median size.

Source: Brain and Valberg (1974).

exposed to a relatively constant concentration of asbestos fiber throughout their work day; in other production operations (e.g., insulation, maintenance, and some production), workers are exposed to extremely variable concentrations of asbestos, with most of their cumulative exposure resulting from short duration, but intense, exposures. Implicit in the use of a linear dose-response relationship and average exposures is the concept that the risk of cancer is directly related to the cumulative asbestos exposure received in a period of time, i.e., the effect of an exposure to 100 f/ml for 1 hour is the same as that of 1 f/ml for 100 hours. (This equivalence applies only for short time periods. Because of the time dependence of mesothelioma risk, 100 f/ml for one year is not equivalent to 2 f/ml for 50 years.) Short, intense exposures could have an effect different from longer and lower exposures if clearance mechanisms are altered by very high concentrations of inspired asbestos. Although there are no data that directly address this question, indirect information suggests that the magnitude of the effect is less than the variability between studies with continuous exposure. Henderson and Enterline (1979) found that the excess lung cancer risk for plant-wide maintenance mechanics was only slightly higher (21 percent) than that for production workers, on a unit exposure basis. Curiously, the risk of pneumoconiosis was much less per unit of cumulative exposure among maintenance workers. The similarity of unit exposure risks of insulation workers compared to groups having continuous exposure suggests that the character of their exposure is not important. However, both comparisons depend upon the exposure estimates of the groups in question. Clearly, average exposures are difficult to estimate from episodic exposures and the above numerical similarities may be fortuitous. The unusually low pneumoconiosis risk among mechanics in the Henderson and Enterline (1979) study may be the result of exposure misestimates.

3.17 RELATIVE CARCINOGENICITY OF DIFFERENT ASBESTOS VARIETIES

Whether there is a different carcinogenic response according to fiber type or industrial process is an issue of increasing concern in the understanding of asbestos disease. Considerable controversy has developed as to whether one variety of asbestos (crocidolite) or mineral class (amphibole) is more carcinogenic than another (the serpentine mineral, chrysotile). Great

Britain, Canada, and Sweden have imposed far more rigid standards for crocidolite than other varieties of asbestos. In contrast, the United States has no special standard for any specific asbestos mineral.

Prior to the late 1960s the question was moot, because most epidemiological studies did not accurately characterize the asbestos fiber types used and measurements were not made of fiber concentration by mineral species. Most measurements only characterized the total quantity of dust in the aerosol (in terms of millions of particles per cubic foot) rather than in terms of fiber concentration. This lack of information on fiber exposure by mineral type was recognized at the time of the 1964 New York Academy of Sciences Conference on Asbestos (Whipple and van Reyen, 1965), and a recommendation was made that the importance of fiber type on the risk of developing asbestosis, carcinoma of the lung, and mesothelial tumors be investigated. In the ensuing years, considerable information was developed on the mortality experience of different groups exposed to different varieties of asbestos in different work processes. Unfortunately, the differential unit exposure risk associated with different fiber types is still not completely understood.

3.17.1 Lung Cancer

3.17.1.1 Occupational Studies. Figure 3-7, Table 3-28 and Table 3-10 summarize the information available on the unit exposure risk for lung cancer in 14 different epidemiological studies. The range of the fractional increase in lung cancer per unit asbestos exposure, expressed in terms of f-y/ml, varies by more than two orders of magnitude. What is unique about this variation is that exposures to a single fiber type yield results that differ by nearly 100-fold. One of the highest unit exposure risks was found in a textile plant that used only chrysotile asbestos (Dement et al., 1983b; McDonald et al., 1983a) and the lowest values were found in a large study of chrysotile mine and mill employees (McDonald et al., 1980) and in groups exposed only to chrysotile asbestos in friction products manufacturing (Berry and Newhouse, 1983; McDonald et al., 1984). Similarly, large (10-fold) differences are found in studies ostensibly of the same process, using the same mix and quality of asbestos fibers in different plants of the same company. A study of asbestos cement manufacturing shows one of the highest unit exposure risks (Finkelstein, 1983). Another study (Weill et al., 1979) suggests a risk more than 1/10 as much, while a 10-fold difference in risk appears to exist in two groups working at different periods in a single British Textile facility (Peto, 1980).

There is only one study in which the exposure was solely to amosite asbestos (Seidman, 1984), and the risk was comparable to the risk found in chrysotile textile operations. However, in several groups exposed to a mixture of chrysotile, amosite, and crocidolite in insulation work (Selikoff et al., 1979), the risk was less than that experienced by either chrysotile textile manufacturers or amosite factory workers.

No data exist, in any study, of unit exposure risks to workers exposed solely to crocidolite asbestos. Enterline and Henderson (1973) and Weill et al. (1979) suggest that workers exposed to chrysotile and crocidolite may have a greater lung cancer risk than those exposed to chrysotile alone, perhaps by a factor of two. However, this suggestion is based on air concentrations of total particles in the respective work environments (including much other dust) and a significant amount of crocidolite could also have been present without affecting the total particle count.

The wide divergence of risks according to fiber type, and even among similar work processes, suggests that factors other than mineral type substantially influenced the studies reviewed. These other factors could include errors in the estimation of exposures that occurred decades previously, biases or other limitations in epidemiological studies describing the disease experience, and statistical uncertainties associated with a limited number of deaths.

While the above factors undoubtedly contribute to some of the observed variability in Figure 3-7, certain consistent differences are likely to be real. Chrysotile textile production imparts a significantly higher risk per fiber exposure than chrysotile mining or friction products manufacturing. The data supporting this suggestion are very convincing for mining versus textiles. They are less convincing for friction products versus textiles because of greater uncertainties in the mortality experience of friction product workers and estimates of their fiber exposure.

McDonald et al. (1984) and others suggested that differences in risk may be caused by differences in fiber size and dynamics of penetration. As chrysotile is processed, the percentage of long curly fibers (which are easily counted but not easily inspired) decreases and the percentage of shorter, straighter, and narrower fibers increases.

3.17.1.2 Environmental Exposures. Data on the risk of lung cancer by fiber type from non-occupational exposures to asbestos are extremely scarce. Siemiatycki (1982) reported on the mortality experience of the general population of Asbestos and Thetford Mines, Quebec. These two areas account for the great preponderance of chrysotile mining in Canada. The female population in these towns has experienced substantial exposure compared to that of individuals in non-mining areas. Data from Gibbs et al. (1980) indicate that recent town air concentrations range from 170 to 3500 ng/m^2. Additionally, home exposures to the wives of workers in the plant also occurred. Table 3-34 lists the mortality experience for selected causes among the female population of Asbestos and Thetford Mines during the years 1966-1977. The observed mortality was compared to the mortality experience of the entire Province of Quebec. There is no statistically significant excess of lung cancer among the mining population females compared to that expected. However, the use of the entire Province of Quebec as the reference population appears to be inappropriate, although the degree of inappropriateness is difficult to ascertain. Lung cancer rates in rural areas are considerably lower than those of urban centers. McDonald et al. (1971) stated that the lung cancer rate for males in the counties surrounding the mining area is two-thirds that of the Province as a whole. Table 3-20 gives the regional lung cancer incidence rates in Quebec Province for males and females for the years 1969-1973. The rate for males in rural counties is 73 percent of the rate in the Province, in agreement with McDonald et al. (1971); however, the relative rates for rural females is even lower, 62 percent of the Provincial rate. Thus, a female lung cancer relative risk of 1.06 compared to Quebec Province translates into a 70 percent increase compared to all of Quebec except Montreal and Quebec City.

TABLE 3-34. MORTALITY FROM SELECTED CAUSES IN ASBESTOS AND THETFORD MINES COMPARED TO QUEBEC PROVINCE, FEMALES, 1966-77.

Cause	O	E	O-E	L.C.L.[a]	O/E	U.C.L.[a]
All causes	1130	1274.6	-144.6	0.84	0.89	0.94
All cancers	289	318.1	-29.1	0.81	0.91	1.02
Digestive cancer	117	110.7	6.3	0.88	1.06	1.28
Respiratory cancer	23	21.5	1.5	0.68	1.07	1.61
Other respiratory diseases	30	51.8	-21.8	0.39	0.58	0.83

[a] 95 percent confidence limits.

Source: Siemiatycki (1982).

This increase is also compatible with data published by Wigle (1977) on cancer mortality in relation to asbestos in municipal water supplies. He compared the cancer risk, by site, for Asbestos and Thetford Mines with nearby communities having moderate concentrations of asbestos in their water supply, and with various other communities throughout the Province of Quebec, including some in populated and industrial areas. The relative cancer risk for females was 1.3 for Asbestos and Thetford Mines, 0.7 for five nearby towns, and 0.8 for other communities (some urban or industrial).

The increases indicated by the adjusted relative risks in Siemiatycki's (1982) study and those indicated by Wigle's (1977) data are both statistically significant. However, these data are only indicative and do not demonstrate an increased lung cancer risk due to environmental asbestos exposure, because the effect of confounding variables was not explored. Nevertheless, the data show that population comparisons between residents of Asbestos and Thetford Mines and other regions of Quebec cannot be used to indicate the absence of a risk.

3.17.2 Mesothelioma

3.17.2.1 Occupational Exposures. Table 3-31 lists values characterizing the risk of death from mesothelioma and lung cancer per f-y/ml in four studies, along with cruder estimates of the mesothelioma risk compared to that of lung cancer in 14 studies. One noticeable feature among all studies is that the ratios of the unit exposure risks of mesothelioma and lung cancer are very similar, irrespective of the type of exposure experienced. Thus, it appears that the same factors affect the variability of mesothelioma risk as affect lung cancer risk, and that mesothelioma risk can be estimated from values of K_L and an average ratio of K_M/K_L. Again, it appears impossible to separate the effect of mineral type from other factors contributing to the variability of potency.

In order to make a broader comparison of mesothelioma according to exposure by mineral type, the risk of pleural and peritoneal mesothelioma can be compared with that of lung cancer in a variety of studies. Because the asbestos risk of lung cancer is directly proportional to the underlying risk of lung cancer, the comparisons are most appropriately made to a lung cancer risk that is standardized to a similar background. In particular, one would expect the ratio of mesothelioma to excess lung cancer among women to be several

TABLE 3-35. RISK OF DEATH FROM MESOTHELIOMA AS A PERCENTAGE OF EXCESS LUNG CANCER, ACCORDING TO FIBER EXPOSURE

Study and fiber type	Obs. O	Exp. E	Lung Cancer O-E	Adj.		Mesothelioma Pl.	Per.	Tot.	Mesothelioma as a % of excess of lung cancer Pl./O-E	Per./O-E	Tot./O-E
Chrysotile											
Acheson et al. (1982)	6	4.5	1.5	5.5		1	0	1	18.2	0.0	18.2
Dement et al. (1983a,b)*	33	9.8	23.2	18.5		0	1	1	0.0	5.4	5.4
McDonald et al. (1983a)	59	29.6	29.4	15.4		0	1	1	0.0	6.5	6.5
McDonald et al. (1980)	230	184.0	46.0	126.2	(166)^a	10(20+)^a	0	10(20+)	7.9(12.0+)	0.0	7.9(12.0+)
Nicholson et al. (1979)*	25	11.1	13.9	17.2		1	0	1	5.8	0.0	5.8
McDonald et al. (1984)	73	49.1	23.9	24.8	(0.0)^b	0(3)^b	0	0(3)	0.0(very high)	0.0	0.0(very high)
Rubino et al. (1979)	9	8.7	0.3	0.3		1	0	1	333.3	0.0	333.3
Weiss (1977)	4	4.3	-0.3	-0.3		0	0	0	0.0	0.0	0.0
Totals (excluding * studies)				147.1		12	1	13	8.2	0.7	8.8
Totals (adj. for additional cases)				187		25	1	26	13.4+	0.5	14.0+
Predominantly chrysotile (>98%)											
McDonald et al. (1983b)	53	50.5	2.5	18.0		10	4	14	55.6	22.2	77.8
Robinson et al. (1979)	49	36.1	12.9	28.4		4	5	13	14.1	17.6	45.8
Robinson et al. (1979)	14	1.7	12.3	123.0	(20)^c	1	1	4	5.0	5.0	20.0
Mancuso [illegible] attar (1967)	33	14.8	18.2	28.3		1	8	9	35.3	28.3	31.8
Peto (19[illegible]	30	15.5	14.5	12.0		7	0	7	58.3	0.0	58.3
Thomas et al. (1982)	22	25.8	-3.8	-3.8		2	0	2	--	--	--
Totals (some unknown duplications of deaths)				102.9		25	18	49	24.3	17.5	47.6
Amosite											
Acheson et al. (1984)	57	29.1	27.9	25.4		4	1	5	15.7	3.9	19.7
Seidman et al. (1979)	83	21.9	61.1	61.1		7	7	14	11.5	11.5	22.9
Totals				86.5		11	8	19	12.7	9.2	22.0
Predominantly crocidolite											
Acheson et al. (1982)	13	6.6	6.4	24.0		3	2	5	12.5	8.3	20.8
Hobbs et al. (1980)	60	38.2	21.8	21.8		17	0	17	78.0	0.0	78.0
Jones et al. (1980)	12	6.3	5.7	21.0		13	4	17	61.9	19.0	81.0
Wignall & Fox (1982)	10	3.7	6.3	23.2		9	3	12	38.8	12.9	57.7
McDonald & McDonald (1978)	7	2.4	4.6	16.8		3	6	9	17.9	35.7	53.6
Totals			1 106.8			45	13	68	42.1	12.2	63.7

TABLE 3-35. (continued)

Study and fiber type	Obs. O	Exp. E	Lung Cancer O-E	Adj.	Mesothelioma Pl.	Mesothelioma Per.	Mesothelioma Tot.	Mesothelioma as a % of excess of lung cancer Pl./O-E	Mesothelioma as a % of excess of lung cancer Per./O-E	Mesothelioma as a % of excess of lung cancer Tot./O-E
Anthophyllite										
Meurman et al. (1974)	21	12.6	8.4	13.4	0	0	0	0.0	0.0	0.0
Totals				13.4	0	0	0	0.0	0.0	0.0
Talc (Tremolite)										
Kleinfeld et al. (1974)	13	4.5	8.5	16.1	0	1	1	0.0	6.2	6.2
Brown et al. (1979)	9	3.3	5.7	8.6	0	0	1	0.0	0.0	11.6
Totals				24.7	0	1	2	0.0	4.0	8.1
Mixed exposures										
Albin et al. (1984)	12	6.6	5.4	12.2	4	0	4	32.8	0.0	32.8
Berry & Newhouse (1983) (M)	143	139.5	3.5	3.5	8	0	8	514.3	0.0	514.3
Berry & Newhouse (1983) (F)	6	11.3	-5.3	-5.3	2	0	2	--	--	--
Clemmesen & Hjalgrim-Jensen (1981)	47	27.3	19.7	26.2	3	0	3	11.5	0.0	11.5
Elmes & Simpson (1977)	27	5.0	22.0	59.4	8(19)[d]	5	24	32.0	8.4	40.4
Finkelstein (1983)	20	3.3	16.7	15.9	6	5	11	37.7	31.4	69.2
Henderson & Enterline ((1979)	63	23.3	39.7	59.6	5	0	170	8.6	44.1	8.4
Selikoff et al. (1979) (US)	390	93.7	296.3	259	61	109	170	23.6	42.1	65.6
Selikoff et al. (1979) (NY-NJ)	93[e]	13.1	79.9	106	11	27	38	10.4	25.5	35.8
Kleinfeld et al. (1967)	10	1.4	8.6	14.4	1	2	3	6.9	13.9	20.8
Kolonel et al. (1980)	13	7.5	5.5	7.3	10	0	46	0.0	39.1	0.0
Newhouse & Berry (1979) (M)	103	43.2	58.8	69.1	19	27	46	27.5	39.1	66.6
Newhouse & Berry (1979) (F)	27	3.2	23.8	100	13	8	21	13.0	8.0	21.0
Nicholson (1976a)	27[e]	8.4	18.6	22.6	8	7	0	35.4	0.0	66.4
Puntoni et al. (1979)	123	54.9	68.1	79.1	0	0	0	0.0	0.0	0.0
Rossiter & Coles (1980)*	84	100.3	-16.3	-16.3	--	--	--	--	--	--
Weill (1984)	188	128.0	60.0	79.5	8	1	9	7.5	6.3	13.8
Totals (except * study)				892.2	168	191	359	18.8	21.4	40.2

*One mesothelioma death is included in a larger study of McDonald et al. (1980).

[a] Subsequent to termination of the study, many additional cases of mesothelioma developed. Four occurred in 1976 and 1977 (McDonald and Liddell, 1979) and six were found in one mining area in 90 consecutive autopsies during 1981-83. (Churg et al., 1984). To account for some of this increase, the additional 10 mesothelioma cases were included and the adjusted excess lung cancer deaths increased by 40 to account for mortality over the 5 additional years. The effect of considering these additional cases is illustrated by data in parentheses.

[b] No mesothelioma cases were found in the cohort. However, three deaths from mesothelioma were identified in the Connecticut Tumor Registry from the plant (Teta et al., 1983). These are included in parentheses for the purposes of this analysis. While a high lung cancer risk was noted in the cohort, the absence of a dose-response relationship made attribution of the cause difficult and no lung cancer deaths were attributed to asbestos exposure.

[c] The adjusted excess lung cancer risk is unrealistically high. A value of 20 will be used.

[d] Eleven deaths were either from pleural mesothelioma or lung cancer. In this analysis, all were considered mesothelioma.

[e] Best estimate data on the cause of death.

times higher than among men because of the greater background risk of lung cancer among men. Table 3-35 lists the various studies from Table 3-2. In each study, an attempt was made to estimate an excess lung cancer risk that would have occurred if the U.S. male rates in 1970 had prevailed for the study population. For example, the standardized number of deaths in women was calculated by multiplying the number of observed deaths minus the expected number of deaths by the ratio of the age standardized male to female lung cancer rate. Similar adjustments were made to the excess number of lung cancers of cohorts followed for long periods of time, that would have had an average time of death earlier than 1970. Adjustments were also made where the lung cancer rates of other nations differed from those in the United States. The last two adjustments led to only minor changes in most cohorts, while the adjustment for gender was substantial and uncertain because of absence of information about the smoking habits of the study group. Finally, adjustments to local rates were made similar to those in Section 3.9. After all the adjustments were made, the ratio of mesothelioma was calculated by type of fiber exposure as a percentage of adjusted excess lung cancer. The results were summed and the combined data for specific mineral exposures were obtained.

There are several limitations to consider when reviewing these data. Because of possible bias caused by underdiagnosis of peritoneal mesothelioma in many cohorts, the principal focus should be on the ratios of pleural mesothelioma to adjusted excess lung cancer. Tissue specimens of all abdominal tumors were reviewed in only a few studies (Selikoff et al., 1979; Seidman, 1984; Newhouse and Berry, 1979; Finkelstein, 1983) to determine if peritoneal mesothelioma had been misdiagnosed. Because of the ongoing review of mesotheliomas in Canada by the McDonalds (McDonald and McDonald, 1978; McDonald et al., 1970, 1971), the study of Canadian miners and gas mask workers can also be considered to have benefited from review. These studies account for 194 of 236 identified peritoneal mesotheliomas. Substantial bias may also exist because of studies in which the tracing of the cohort is limited; in some studies as many as 39 percent of the exposed individuals were untraced. The inadequacy of tracing was particularly high in studies of workers exposed to crocidolite. The danger is that mesotheliomas were identified in registries because of their uniqueness, but that lung cancers in untraced individuals were not. Thus, it is likely that there is a substantial overestimate of the number of mesotheliomas relative to lung cancer associated with crocidolite exposures. Also, the comparison of the ratio of mesothelioma to excess lung cancer is uncertain because of substantially different time courses for the two diseases. The time course for lung cancer is determined by the time course of the underlying risk, which is usually the time course of lung cancer from cigarette smoking. On the other hand, the time course for mesothelioma is strictly dependent upon the time from onset of exposure, rising at about the fourth or fifth power of time from first exposure. The analysis utilized in Table 3-35 does not fully account for such differences.

In comparing the different ratios of pleural mesothelioma to adjusted lung cancer for all studies in which the major exposure was to one fiber type, the ratios for chrysotile, amosite, and mixed exposures are roughly comparable. Crocidolite exposures have a twofold to threefold greater number of pleural mesotheliomas relative to excess adjusted lung cancer. However, as noted previously, the untraced individuals in the various crocidolite cohorts may have led to an overestimate of this ratio. The possibility of underdiagnosis of mesothelioma notwithstanding, the risk of peritoneal mesothelioma is much lower with pure chrysotile exposures than with amphiboles or mixed exposure. Only one peritoneal mesothelioma has been identified among more than 25 mesotheliomas in chrysotile-exposed populations. Though a greater mesothelioma potency may be considered for crocidolite (a factor of two or four considering both pleural and peritoneal sites), the effect of other factors in a given exposure circumstance leads to much greater differences, as for example in the case of lung cancer, where different exposure circumstances with the same fiber lead to nearly 100-fold differences in unit exposure risk. A similar situation exists with mesothelioma where the manufacture of amosite insulation is associated with a high risk of mesothelioma (see Table 3-34), while amosite mining demonstrates little excess risk (Webster, 1978; Solomons, 1984). Also, great differences in risk appear to exist between the crocidolite mines of the Transvaal and those of the Cape Province. Thus, any suggestion that there are dramatic differences between asbestos varieties has to be considered in the light of greater differences that appear to be related to processing, fiber size distribution effects within a single asbestos variety (e.g., the difference between textiles and mining), and to differences between cohort studies of the same exposure circumstances (e.g., the asbestos cement studies of Weill et al. (1979) and of Finkelstein (1982, 1983), or the two cohorts of Peto (1980).

There was no evidence in Table 3-10 of a substantial difference in lung cancer unit exposure risk attributable to fiber type. While a pure amosite exposure had a unit exposure risk about twice that of chrysotile exposures, the combination of amosite or crocidolite with chrysotile in other exposure circumstances demonstrated lower unit exposure risks. The data from Tables 3-31 and 3-35 indicate the crocidolite mesothelioma to lung cancer risk ratio is no more than four times that of other fibers, and when crocidolite is used with other fibers, the combined ratio differs little from non-crocidolite exposures. These findings suggest that crocidolite or amphibole exposures cannot be the explanation of most mesotheliomas found in some predominantly chrysotile exposure circumstances (e.g., Canadian mining and milling and Rochdale, England textile production). This conclusion is further supported by the observation that all the mesotheliomas in the above circumstances were of the pleura, whereas amphibole exposure generally produces comparable numbers of pleural and peritoneal mesotheliomas (the study of Hobbs et al. (1980) is a remarkable exception). Finally, in the case of the Rochdale factory, the risk of mesothelioma in a factory using only 2.6 percent crocidolite from 1932-1968 (Doll and Peto, 1985) was as high as the risk in the London factory studied by Newhouse and Berry (1979) in which large amounts of crocidolite and amosite were used.

A careful consideration of the role of amphiboles in the production of mesothelioma is important for control of asbestos disease. On the one hand, it would be a mistake to minimize or ignore the mesothelioma risk of chrysotile. Millions of tons of this fiber presently are in building materials and other products. The potential for release in future years is substantial unless proper work practices and care are utilized during repair and maintenance work. On the other hand, it should be recognized that crocidolite, particularly, is a very dangerous asbestos material. This comes from two aspects of the fiber. One is the above-mentioned 2-4 fold greater risk of mesothelioma relative to lung cancer found in crocidolite exposure circumstances. This certainly indicates a greater unit exposure risk for mesothelioma relative to other asbestos fibers. Secondly, the large percentage of thin fibers in a crocidolite aerosol (which may contribute to increased risk mentioned above) also may contribute to a greater fiber exposure when crocidolite-containing products are manufactured or used because these very thin fibers remain aloft for longer periods of time. Considering all factors, the proscription on the use of crocidolite in several countries would appear to be justified. Fortunately, few pure crocidolite exposure circumstances exist in the United States. Subject to their uncertainties, the average values of K_L and K_M reflect the most important processes where crocidolite is a constituent of the material being produced. Nevertheless, if a pure crocidolite exposure is encountered, a mesothelioma risk greater than that estimated using the average value of K_M is likely to exist and correspondingly greater precautions should be exercised.

3.17.2.2 Environmental Exposures. Mesothelioma has been documented in a variety of non-occupational circumstances, including family contacts of asbestos-exposed individuals. Table 3-36 lists observed family contact mesotheliomas associated with three occupational exposure circumstances and mesotheliomas identified in the contact worker group (the observation periods are not quite commensurate). It is important to note that family contact cases are seen with exposure to chrysotile, amosite and crocidolite. By fiber type, there appears to be little difference in the family contact risk relative to the risk at work.

TABLE 3-36. MESOTHELIOMA FROM FAMILY CONTACT IN THREE OCCUPATIONAL CIRCUMSTANCES

Occupation	Country	Fiber type	Mesothelioma Family members	Workers
Miners and millers	Canada	Chrysotile	3[a]	12[b]
Insulation manufacturers	U.S.A.	Amosite	4[c]	14[d]
Mixed products	U.K.	Mixed	9[e]	67[f]

[a] McDonald and McDonald (1980).
[b] McDonald et al. (1980).
[c] Anderson (1976).
[d] Seidman et al. (1979).
[e] Newhouse and Thomson (1965).
[f] Newhouse and Berry (1979).

Animal studies support this conclusion and suggest that all varieties of asbestos should be considered equally potent with respect to the production of either lung cancer or mesothelioma in both inhalation and implantation studies.

As discussed previously, many risk differences may be accounted for by differences in fiber size distributions in different work environments, rather than by fiber type. The greatest percentage of longer and thicker fibers occurs in the work environment of miners and millers. Asbestos used in manufacturing processes is broken apart while it is incorporated into the finished product. During application or removal of insulation products it is further manipulated and the fibers become further reduced in length and diameter with many falling within the range of significant carcinogenic potency (see Section 4-6). Because these shorter and thinner fibers can readily be carried to the periphery of the lung where they penetrate the visceral pleura and lodge in the visceral or parietal pleura, they may be of importance in the etiology of mesothelioma. Bignon, Sebastien, and their colleagues (1978) reported data from a study of lungs and pleura of shipyard workers. Larger fibers, often amphibole, were found in lung tissue. In the pleura, the fibers were generally chrysotile, but shorter and thinner. The early association of mesothelioma with crocidolite occurred because, even in mining, crocidolite is readily broken apart, yielding many fibers in a respirable and carcinogenic size range, and has been extensively used in Great Britain in extremely dusty environments (e.g., spray insulation), creating high exposures for many individuals, with a concomitant high risk of death from mesothelioma. Thus the disease came to attention (Wagner et al., 1960). The mining and milling of chrysotile, on the other hand, involves exposures to long and curly fibers which are easily counted but not easily inspired.

Recent exposures in Turkey to the fibrous zeolite mineral, erionite, have been associated with mesothelioma. Results reported by Baris et al. (1979) demonstrate an extraordinary risk; annual incidence rates of nearly 1 percent exist for mesothelioma. In 1974, 11 of 18 deaths in Karain, Turkey were from this cause. The fiber lengths are highly variable; most erionite fibers are shorter than 5 μm and 75 percent are less than 0.25 μm.

3.18 SUMMARY

Data are available that allow unit risks to be determined for lung cancer and mesothelioma. The values for K_L, the fractional risk per f-y/ml, vary widely among the studies, largely because of the statistical variability associated with small numbers but also because of uncertainties associated with methodology and exposure estimates. Based on an analysis of the unit exposure risk for lung cancer and mesothelioma in 11 studies (all studies for which unit exposure risks can be estimated except chrysotile mining and milling), the best estimate for K_L is 0.010, and for K_M it is 1.0×10^{-8}. An analysis of variability suggests that the 95 percent confidence limit on the estimate of K_L is generally from 0.0040 to 0.027 (a factor of 2.5), but for K_L in an unknown exposure circumstance it is a factor of 10. A greater range of uncertainty applies to the best estimate for the value of K_M, the uncertainty in a given exposure circumstance is also greater, perhaps by a factor of 20. Differences in asbestos type cannot explain the variability of K_L observed in different studies. However, the lower risk values found in chrysotile mining and milling compared with chrysotile textile production suggest that fiber length and width distribution is important. The unit exposure mesothelioma risk also differs greatly in different exposure circumstances, but the ratio of mesothelioma risk to excess lung cancer risk is relatively constant. Peritoneal mesothelioma has largely been associated with amphibole exposure, although this is qualified by the possibility of underdiagnosis in some studies. Pleural mesothelioma is associated with exposure to chrysotile and crocidolite; while differences in pleural mesothelioma risk attributable to fiber type may exist, they are much less than differences attributable to other factors.

4. EXPERIMENTAL STUDIES

4.1 INTRODUCTION

Most animal studies of asbestos health effects have been used to confirm and extend previously established human data rather than to predict human disease. This situation exists because asbestos usage predates the use of animal studies for ascertainment of risk; because some animal models are relatively resistant to the human diseases of concern; and because lung cancer, the principal carcinogenic risk from asbestos, is the result of a multifactorial interaction between causal agents, principally cigarette smoking and asbestos exposure, and is difficult to elicit in a single exposure circumstance. Although all of the asbestos-related malignancies were first identified in humans, experimental animal studies confirmed the identification of the diseases and provided important information, not available from human studies, on the deposition, clearance, and retention of fibers, as well as cellular changes at short times after exposure. Unfortunately, one of the most important questions raised by human studies, that of the role of fiber type and size, is only partially answered by animal research. Injection and implantation studies in animals have shown longer and thinner fibers to be more carcinogenic once in place at a potential site of cancer. However, the size dependence of the movement of fibers to mesothelial and other tissues is not fully elucidated, and the questions raised by human studies concerning the relative carcinogenicity of different asbestos varieties still remain.

4.2 FIBER DEPOSITION AND CLEARANCE

Deposition and clearance of fibers from the respiratory tract of rats were studied directly by Morgan and his colleagues (Morgan et al., 1975; Evans et al., 1973) using radioactive asbestos samples. Following 30-minute inhalation exposures in a nose breathing apparatus, deposition and clearance from the respiratory tract were followed. The distribution of fibers in various organ systems was determined at the conclusion of inhalation, showing that 31-68 percent of inspired fibrous material is deposited in the respiratory tract. The distribution of that deposited material is shown in Table 4-1. Rapid clearance, primarily from the upper respiratory tract (airways above the

TABLE 4-1. DISTRIBUTION OF FIBER AT THE TERMINATION OF 30-MINUTE INHALATION EXPOSURES IN RATS (PERCENT OF TOTAL DEPOSITED)

Fiber	Nasal passages[a]	Esophagus	Gastro-intestinal tract	Lower respiratory tract	Percent deposited[b]
Chrysotile A	9 ± 3	2 ± 1	51 ± 9	38 ± 8	31 ± 6
Chrysotile B	8 ± 2	2 ± 1	54 ± 5	36 ± 4	43 ± 14
Amosite	6 ± 1	2 ± 1	57 ± 4	35 ± 5	42 ± 14
Crocidolite	8 ± 3	2 ± 1	51 ± 9	39 ± 5	41 ± 11
Anthophyllite	7 ± 2	2 ± 1	61 ± 8	30 ± 8	64 ± 24
Fluoramphibole	3 ± 2	1 ± 1	67 ± 5	29 ± 4	68 ± 17

[a] Mean and standard deviation.

[b] Percent of total inspired.

Source: Morgan et al. (1975).

trachea), occurs within 30 minutes; up to two-thirds of the fibers are swallowed and found in the GI tract.

Clearance from the lower respiratory tract (trachea to alveoli) proceeds more slowly and two distinct components of clearance are observed. The first, believed to be caused by macrophage movement, leads to elimination of a considerable portion of the material deposited in the lower respiratory tract at a half life of 6-10 hours. The slower component that follows has a half-life of 60-80 days and involves clearance from the alveolar spaces. Data for a synthetic fluoramphibole (Figure 4-1) show one short-term and two long-term components for clearance of fibers. Other data on the lung content of animals, sacrificed at various times after exposure, show only a single long-term clearance component (Morgan et al., 1978); however, the ratio of fibers in the feces to those in the lung at the time of sacrifice is not a constant, as would be expected from a single exponential clearance mechanism.

By extrapolating curves like that of Figure 4-1 to zero-time for a variety of fibers, it is possible to ascertain the relative amounts of fibers

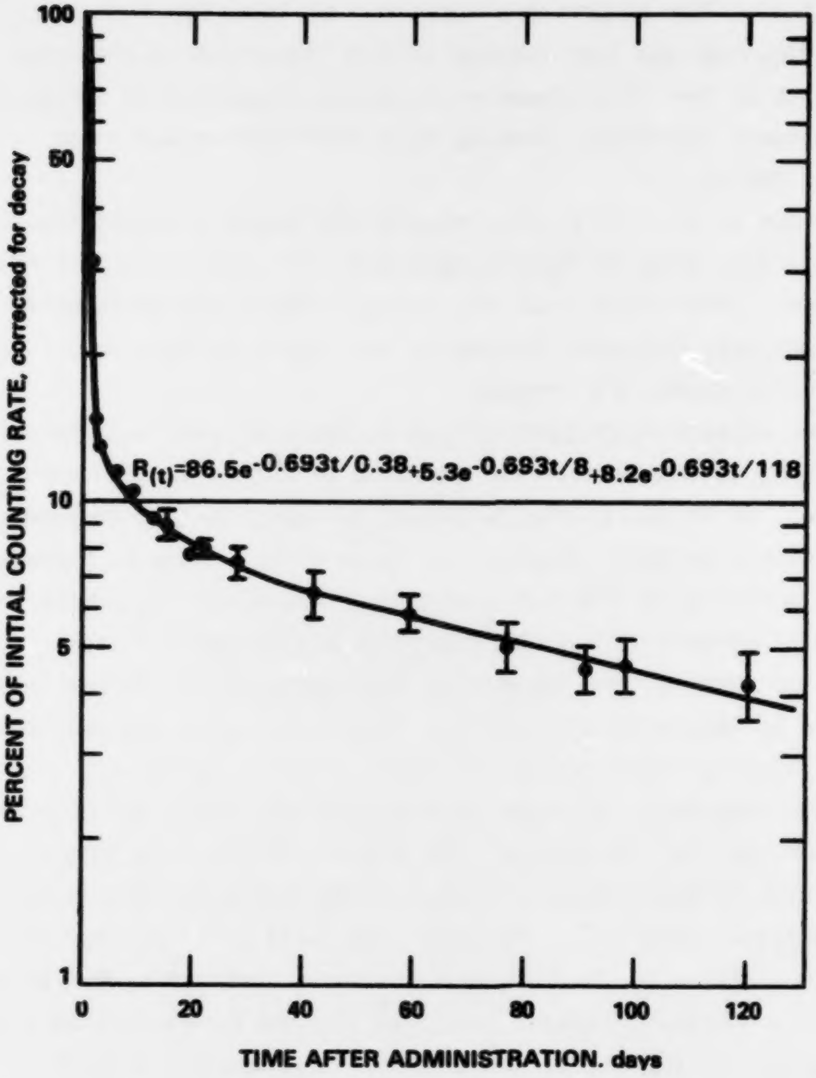


Figure 4-1. Measurements of animal radioactivity (corrected for decay) at various times after inhalation exposure to synthetic fluoramphibole. Mean result for three animals expressed as a percentage of the counting rate measured immediately after exposure.

Source: Morgan et al. (1977).

deposited in the bronchiolar-alveolar spaces. These data are shown for different fibers in Figure 4-2. The relative similarity of the percentage deposited in the lower bronchioles or alveoli for different fiber diameters is a reflection of two competing processes: at lower fiber diameters, the fibers can be inspired and then expired without impaction in the lower respiratory tract, but as the fiber diameter increases, impaction in the upper respiratory tract becomes important, leading to a lower percentage being carried to the alveolar spaces.

Morgan et al. (1978) also studied the length distribution of fibers that remain in the lungs of rats to determine the significance of fiber length on clearance. They found that the shorter fibers are preferentially removed within one week following inhalation and suggested that longer fibers reaching the alveolar spaces are trapped.

The radioactive chrysotile used in the clearance experiments allows autoradiography to demonstrate the location of fibers at different times after exposure. At 48 hours after exposure, the distribution of fibers in the lung is relatively uniform. However, at later times, there is a movement of fibers to the periphery of the lung where they accumulate in subpleural foci consisting of alveoli filled with fiber-containing cells.

Other data on the deposition and retention of inhaled asbestos were reported by Wagner et al. (1974). Figure 4-3 shows the dust content of rat lungs following exposures to different asbestos varieties. In the case of amphibole exposures, a linear increase in the amount of retained fiber was seen, whereas for chrysotile, the content of the lung rapidly reached an equilibrium between removal or dissolution processes and deposition, and did not increase thereafter. The long-term build-up of the amphiboles indicates that, in addition to the clearance processes observed by Morgan et al. (1977), there is a virtual permanent retention of some fibers. Using a minute volume for the rat of 100 ml, it would appear that about 1 percent of the total crocidolite or amosite inhaled is retained permanently in the lung.

The finding of a rapid movement from the upper respiratory tract and a slower clearance from the lower respiratory tract to the GI tract demonstrates a route of exposure that may be important for GI cancer. The observation in humans of peritoneal mesothelioma, of excess cancers of the stomach, colon, and rectum, and possibly of cancers at other non-respiratory sites, such as

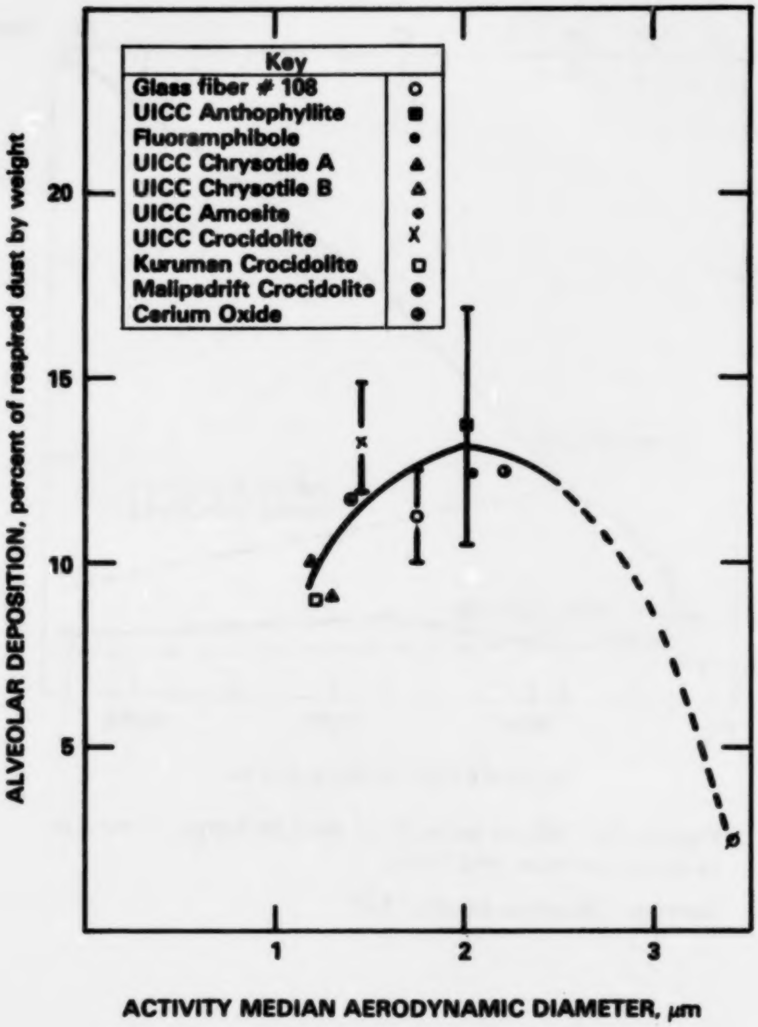


Figure 4-2. Correlation between the alveolar deposition of a range of fibrous and non-fibrous particles inhaled by the rat and the corresponding activity median aerodynamic diameters.
Source: Morgan (1979).

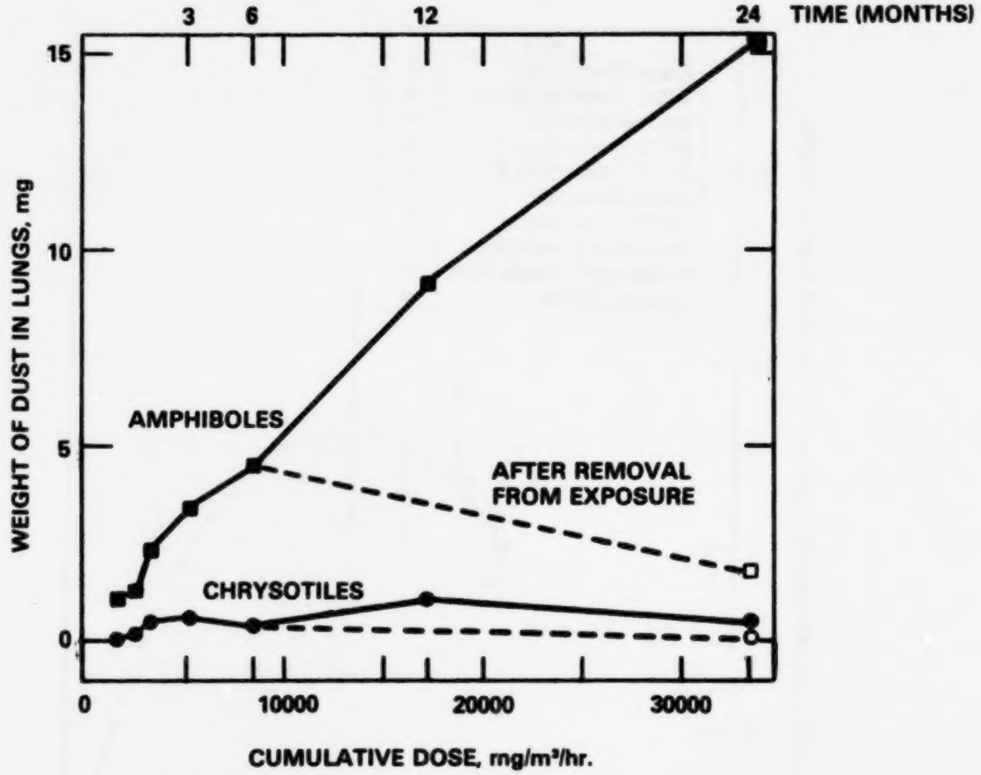


Figure 4-3. Mean weight of dust in lungs of rats in relation to dose and time.

Source: Wagner et al. (1974).

the kidney, could result from the migration of such fibers to and across the gastrointestinal mucosa. Additionally, fibers may reach organs in the peritoneal cavity by transdiaphragmatic migration or lymphatic-hematogenous transport.

4.3 CELLULAR ALTERATIONS

Several studies describe cellular changes in animals following exposure to asbestos. Holt et al. (1964) describe early (14-day) local inflammatory lesions found in the terminal bronchioles of rats following inhalation of asbestos fibers. These lesions consist of multi-nucleated giant cells, lymphocytes, and fibroblasts. Progressive fibrosis follows within a few weeks of the first exposure to dust. Davis et al. (1978) describe similar early lesions found in rats, consisting of a proliferation of macrophages and cell debris in the terminal bronchioles and alveoli.

Jacobs et al. (1978) fed rats 0.5 mg or 50 mg of chrysotile daily for 1 week or 14 months and subsequently examined GI tract tissue by light and electron microscopy. No effects were noted in the esophagus, stomach, or cecal tissue, but structural changes in the ileum were seen, particularly of the villi. Considerable cellular debris was detected in the ileum, colon, and rectal tissue by light microscopy. Electron microscopy data confirm the light microscopy data and indicate that the observed changes are consistent with a mineral-induced cytotoxicity.

A single oral administration of 5-100 mg/kg of chrysotile to rats produces a subsequent increase in thymidine in the stomach, duodenum, and jejunum (Amacher et al., 1975), suggesting that an immediate response of cellular proliferation and DNA synthesis may be stimulated by chrysotile ingestion.

4.4 MUTAGENICITY

Many studies showed asbestos not to be mutagenic, e.g., in *Escherichia coli* and *Salmonella typhimurium* tester strains (Chamberlain and Tarmy, 1977). Newman et al. (1980) reported that asbestos has no mutagenic ability in Syrian hamster embryo cells, but may increase cell permeability and allow other mutagens into the cell. Mossman et al. (1983) showed that UICC (Union Intranationale Contra le Cancer) crocidolite and chrysotile do not produce DNA strand breaks in the alkyline elution assay when applied to cultured hamster tracheal cells. Similar negative results were obtained by Lechner et al. (1983) with respect to induction of DNA strand breakage in human bronchial organ cultures treated with UICC chrysotile, amosite, and crocidolite. Finally, Hart et al. (1979) demonstrated that asbestos does not produce unscheduled DNA synthesis in human fibroblasts or single or double strand breaks.

However, a few studies do show mutagenicity. Sincock (1977) used several chrysotile, amosite, and crocidolite samples to show that an increased frequency of polyploids and cells with fragments results from passive inclusion of asbestos in the culture media of Chinese hamster ovary (CHO)-K1 cells. Similarly, Lavappa et al. (1975) showed that chrysotile induced a significant and exposure-related increase in chromosome aberrations in cultured Syrian hamster embryo cells. Amosite, chrysotile, and crocidolite were found to be weakly mutagenic in Chinese hamster lung cells in the 6-thioguanine-resistance assay (Huang, 1979). Livingston et al. (1980) showed that exposure to crocidolite and amosite can increase the sister chromatid exchange rate in Chinese hamster ovarian fibroblasts.

The evidence for chromosomal effects in human cells is contradictory. Valerio et al. (1980) found that freshly isolated lymphocytes undergo chromosomal changes when treated with UICC Rhodesian chrysotile. In contrast, Sincock et al. (1982) found negative effects with lymphocytes exposed to UICC crocidolite. Asbestos was shown to be highly cytotoxic in a variety of preparations (e.g., Mossman et al., 1983; Chamberlin and Brown, 1978).

In summary, while some evidence exists for aneuploidy caused by asbestos, most studies show that asbestos probably is not mutagenic in the classic sense of causing gene mutations and/or chromosomal breakage.

4.5 INHALATION STUDIES

The first unequivocal data that showed a relationship between asbestos inhalation and lung malignancy in laboratory animals were those of Gross et al. (1967) who observed carcinomas in rats exposed to a mean concentration of 86 mg/m^3 chrysotile for 30 hours a week from the age of 6 weeks. Of 72 rats surviving for 16 months or longer, 19 developed adenocarcinomas, 4 developed squamous cell carcinomas, and 1 developed a mesothelioma. No malignant tumors were found in 39 control animals. A search was made for primaries at other sites which could have metastasized and none were found. These and other data are summarized in Table 4-2.

Reeves et al. (1971) found two squamous cell carcinomas in 31 rats sacrificed after 2 years following exposure to about 48 mg/m^3 of crocidolite. No malignant tumors were reported in rabbits, guinea pigs, or hamsters, or in animals exposed to similar concentrations of chrysotile or amosite. No details of the pathological examinations were given.

In a later study (Reeves et al., 1974), malignant tumors developed in 5 to 14 percent of the rats that survived 18 months after exposure. Lung cancer and mesothelioma were produced by exposures to amosite and chrysotile, and lung cancer was produced by crocidolite inhalation. Again, significant experimental details were not provided; information on survival times and times of sacrifice would have been useful. Available details of the exposures and results are given in Table 4-3. While the relative carcinogenicity of the fiber types was similar, the fibrogenic potential of chrysotile, which had been substantially reduced in length and possibly altered by milling (Langer et al., 1978), was much less than that of the amphiboles. These results are also discussed in a later paper by Reeves (1976).

The most important series of animal inhalation studies is that of Wagner et al. (1974, 1977). Wagner exposed 849 Wistar SPF rats to the five UICC asbestos samples at concentrations from 10.1 to 14.7 mg/m^3 for times ranging from 1 day to 24 months. These concentrations are typically 10 times those measured in dusty asbestos workplaces during earlier decades. For all the exposure times, 50 adenocarcinomas, 40 squamous-cell carcinomas, and 11 mesotheliomas were produced. All varieties of asbestos produced mesothelioma and lung malignancies, in some cases from exposures as short as 1 day. Data from these experiments are presented in Tables 4-4 and 4-5. These tumors follow a reasonably good linear relationship for exposure times of 3 months or greater. However, the incidence in the 1-day exposure group is considerably greater than expected. Exposure had a limited effect on length of life. Average survival times varied from 669 to 857 days for exposed animals versus 754 to 803 days for controls. The development of asbestosis is also documented. There are 17 lung tumors, 6 in rats with no evidence of asbestosis and 11 in rats with minimal or slight asbestosis. Cancers at extrapulmonary sites are listed. Seven malignancies of ovaries and eight malignancies of male genitourinary organs were observed in the exposed groups of approximately 350 male

TABLE 4-2. SUMMARY OF EXPERIMENTS ON THE EFFECTS OF INHALATION OF ASBESTOS

Study	Animal species	Material administered	Dosage	Animals Examined for tumors	Findings (malignant tumors)	Average survival time
Gross et al. (1967)	132 male white rats	Ball- and hammer-milled Canadian chrysotile with/without 0.05 ml intratracheal 5 percent NaOH	42-146 mg/ml (mean concentration, 86 mg/m^3) for 30 hours/week	72	17 adenocarcinomas 4 squamous-cell sarcomas 7 fibrosarcomas 1 mesothelioma	not available
	55 male white rats	Controls with/without 5 percent NaOH	control	39	none	not available
Reeves et al. (1971)	206 rats 106 rabbits 139 guinea pigs 214 hamsters	Ball-milled chrysotile, amosite, and crocidolite	48±2 mg/m^3 for 16 hours/week up to 2 years	not available	2 squamous-cell carcinomas in 31 animals from crocidolite exposure	no information periodic sacrifices were made
Reeves et al. (1974)	219 rats 216 gerbils 100 mice 72 rabbits 108 guinea pigs	Ball- and hammer-milled chrysotile, amosite, and crocidolite	48±2 mg/m^3 for 16 hours/week up to 2 years	120 rats 116 gerbils 10 mice 30 rabbits 43 guinea pigs	10 malignant tumors in rats, 2 in mice (Table 4-3)	no information periodic sacrifices were made
Wagner et al. (1974)	13 groups of approximately 50, and 15 of about 25 Wistar SPF rats	Amosite, anthophyllite, crocidolite, Canadian chrysotile, Rhodesian chrysotile (UICC samples)	10.1 to 14.7 mg/m^3 for 1 day to 24 months, 35 hours/week	849	(See Tables 4-4 and 4-5) All asbestos varieties produced mesothelioma and lung cancer, some from exposure as short as 1 day	669 to 857 days versus 754 to 803 for controls. Survival times not significantly affected by exposure.
Wagner et al. (1977)	CO Wistar male and female rats	Superfine chrysotile	10.8 mg/m^3 37.5 hours/week for 3, 6, or 12 months		1 adenocarcinoma of the lung in 24 animals exposed for 12 months	
	CO Wistar male and female rats	Nonfibrous cosmetic talc			none	
Davis et al. (1978)	46 groups of approximately 20 Han SPF rats and 20 Han SFP rats	UICC samples of amosite, chrysotile, and crocidolite	2 mg/m^3 and 10 mg/m^3 35 hours/week for 224 days	208	7 adenocarcinomas 3 squamous-cell sarcomas, 1 pleural mesothelioma, 1 peritoneal mesothelioma	not available sacrificed at 29 months
	20 Han SPF rats	control	control	20	none	

TABLE 4-3. EXPERIMENTAL INHALATION CARCINOGENESIS IN RATS AND MICE

Fiber	Exposure[a]		Rats		Mice	
	Mass mg/m^3	Fiber f/ml	Animals examined	Malignant tumors	Animals examined	Malignant tumors
Chrysotile	47.9	54	43	1 lung papillary carcinoma 1 lung squamous-cell carcinoma 1 pleural mesothelioma	19	None
Amosite	48.6	864	46	2 pleural mesotheliomas	17	None
Crocidolite	50.2	1,105	46	3 squamous-cell carcinomas 1 adenocarcinoma 1 papillary carcinoma - all of the lung	18	2 papillary carcinomas of bronchus
Controls			5	None	6	1 papillary carcinoma of bronchus

[a] The asbestos was comminuted by vigorous milling, after which 0.08 to 1.82% of the airborne mass was of fibrous morphology (3:1 aspect ratio) by light microscopy.

Source: Reeves et al. (1974).

TABLE 4-4. NUMBER OF RATS WITH LUNG TUMORS OR MESOTHELIOMAS AFTER EXPOSURE TO VARIOUS FORMS OF ASBESTOS THROUGH INHALATION

Form of Asbestos	Number of animals	Adenocarcinomas	Squamous-cell carcinomas	Mesotheliomas
Amosite	146	5	6	1
Anthophyllite	145	8	8	2
Crocidolite	141	7	9	4
Chrysotile (Canadian)	137	11	6	4
Chrysotile (Rhodesian)	144	19	11	0
None	126	0	0	0

Source: Wagner et al. (1974)

TABLE 4-5. NUMBER OF RATS WITH LUNG TUMORS OR MESOTHELIOMAS AFTER VARIOUS LENGTHS OF EXPOSURE TO VARIOUS FORMS OF ASBESTOS THROUGH INHALATION

Length of exposure	Number of animals tested	Number of animals with lung carcinomas	Number of animals with pleural mesotheliomas	Percent of animals with tumors
None	126	0	0	0.0
1 day	219	3[a]	2[b]	2.3
3 months	180	8	1	5.0
6 months	90	7	0	7.8
12 months	129	35	6	31.8
24 months	95	37	2	41.0

[a] Two rats exposed to chrysotile and one to crocidolite.

[b] One rat exposed to amosite and one to crocidolite.

Source: Wagner et al. (1974).

and female rats. No malignancies were observed in control groups of 60 males and females. The incidence of malignancy at other sites varied little from that of the controls. The authors note that if controls from other experiments in which ovarian and genitourinary tumors were present are included, the comparative incidence in the exposed groups in the first study lacks statistical significance. No data are provided on the variation of tumor incidence at extrapulmonary sites with asbestos dosage.

Wagner et al. (1977) also compared the effects of inhalation of a superfine chrysotile to the effects of inhalation of a pure nonfibrous talc. One adenocarcinoma was found in 24 rats exposed to 10.8 mg/m^3 of chrysotile for 37.5 hours a week for 12 months.

In a study similar to Wagner's, Davis et al. (1978) exposed rats to 2.0 or 10.0 mg/m^3 of chrysotile, crocidolite, and amosite (equivalent to 430 to 1950 f/ml). Adenocarcinomas and squamous-cell carcinomas were observed in chrysotile exposures, but not in crocidolite or amosite exposures (Table 4-6). One pleural mesothelioma was observed with crocidolite exposure, and extrapulmonary neoplasms included a peritoneal mesothelioma. A relatively large number of peritoneal connective tissue malgnancies also were observed, these including a leimyofibroma on the wall of the small intestine. The meaning of these tumors is unclear.

TABLE 4-6. EXPERIMENTAL INHALATION CARCINOGENESIS IN RATS

	Exposure			
	Mass mg/m^3	Fiber f>5μm/ml	Number of animals examined	Malignant tumors
Chrysotile	10	1,950	40	6 adenocarcinomas 2 squamous-cell carcinomas
Chrysotile	2	390	42	1 squamous-cell carcinoma 1 peritoneal mesothelioma
Amosite	10	550	43	None
Crocidolite	10	860	40	None
Crocidolite	5	430	43	1 pleural mesothelioma
Control			20	None

Source: Davis et al. (1978).

Inhalation exposures result in concomitant GI exposures from the asbestos that is swallowed after clearance from the bronchial tree. Although all inhalation experiments focus on thoracic tumors, those of Wagner et al. (1974), Davis et al. (1978), and, to a limited extent, Gross et al. (1967) also include a search for tumors at extrathoracic sites. A limited number of these tumors were found, but no association could be made with asbestos exposure.

One important aspect of the inhalation experiments is the number of pulmonary neoplasms that can be produced by inhalation in the rat as compared to other species (Reeves et al., 1971, 1974). This phenomenon illustrates the variability of species response to asbestos and the need for an appropriate model before extrapolations to man can be made with confidence. The absence of significant GI malignancy from asbestos exposure in animals, in contrast to that found in humans, may be the result of the use of inappropriate animal models.

4.6 INTRAPLEURAL ADMINISTRATION

Evidence that intrapleural administration of asbestos results in mesothelioma was presented in 1970 when Donna (1970) produced mesotheliomas in Sprague-Dawley rats treated with a single dose of 67 mg of chrysotile, amosite, or crocidolite. Reeves et al. (1971) produced mesothelial tumors in rats (1 of 3 with crocidolite and 2 of 12 with chrysotile) by intrapleural injection of 10 mg of asbestos. Two of 13 rabbits injected with 16 mg of crocidolite developed mesotheliomas.

In a series of experiments, Stanton and Wrench (1972) demonstrated that major commercial varieties of asbestos, as well as various other fibers, produce mesotheliomas in as many as 75 percent of animals into which material had been surgically implanted onto the pleural surface. The authors conclude that the carcinogenicity of asbestos and other fibers is strongly related to their physical size; fibers that have a diameter of less than 3 μm are carcinogenic and those that have a larger diameter are not carcinogenic. Further, samples treated by grinding in a ball mill to produce shorter length fibers are less likely to produce tumors. Although the authors attribute the reduced carcinogenicity to a shorter fiber length, the question was raised of the effect of the destruction of crystallinity, and perhaps other changes in the fibers, caused by the extensive ball milling (Langer et al., 1978).

Since 1972, Stanton and his co-workers (Stanton et al., 1977, 1981) have continued these investigations of the carcinogenic action of durable fibers. Table 4-7 summarizes the results of 72 different experiments. In their analyses, Stanton et al. (1981) suggest that the best measure of carcinogenic potential is the number of fibers that measure ≤ 0.25 µm in diameter and ≥ 8 µm in length, although a good correlation of carcinogenicity is also obtained for fibers ≤ 1.5 µm in diameter and ≥ 4 µm in length. The logit distribution of tumor incidence against the log of the number of particles having a diameter ≤ 0.25 µm and length ≥ 8 µm is shown in Figure 4-4. The regression equation for the dotted line is

$$\ln[p/(1-p)] = -2.62 + 0.93 \log x \tag{4-1}$$

where p is the tumor probability and x is the number of particles per µg that are ≤ 0.25 µm diameter and ≥ 8 µm long. A reasonable relationship exists between the equation and available data, but substantial discrepancies suggest the possibility that other relationships may better fit the data. Bertrand and Pezerat (1980) suggested that carcinogenicity may correlate as well with the ratio of length to width (aspect ratio).

Another comprehensive set of experiments was conducted by Wagner et al. (1973, 1977). Mesothelioma was produced from intrapleural administration of asbestos to CD Wistar rats, demonstrating that there is a strong dose-response relationship. Tables 4-8 and 4-9 list the results of these experiments.

Pylev and Shabad (1973) and Shabad et al. (1974) reported mesotheliomas in 18 of 48 rats and in 31 of 67 rats injected with 3 doses of 20 mg of Russian chrysotile. Other experiments by Smith and Hubert (1974) produced mesotheliomas in hamsters injected with 10-25 mg of chrysotile, 10 mg of amosite or anthophyllite, and 1-10 mg of crocidolite.

Various suggestions have been made that the natural oils and waxes contaminating asbestos fibers might be related to the carcinogenicity of asbestos fibers (Harington, 1962; Harington and Roe, 1965; Commins and Gibbs, 1969). However, this theory was not substantiated in the experiments performed by Wagner et al. (1973) or Stanton and Wrench (1972).

TABLE 4-7. SUMMARY OF 172 EXPERIMENTS WITH DIFFERENT FIBROUS MATERIALS

Experiment	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/μg ≤0.25 μm diameter x ≥8 μm long	Experiment	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/μg ≤0.25 μm diameter x ≥8 μm long
1	Titanate 1	21/29	95±4.7	4.94	37	Halloy 1	4/25	20±9.0	0
2	Titanate 2	20/29	100	4.70	38	Halloy 2	5/28	23±9.3	0
3	Silcarbide	17/26	100	5.15	39	Glass 8	3/26	19±10.3	3.01
4	Dawson 5	26/29	100	4.94	40	Crocid 11	4/29	19±8.5	0
5	Tremolite 1	22/28	100	3.14	41	Glass 19	2/28	15±9.0	0
6	Tremolite 2	21/28	100	2.84	42	Glass 9	2/28	14±9.4	1.84
7	Dawson 1	20/25	95±4.8	4.66	43	Alumin 6	2/28	13±8.8	0.82
8	Crocid 1	18/27	94±6.0	5.21	44	Dawson 6	3/30	13±6.9	0
9	Crocid 2	17/24	93±6.5	4.30	45	Dawson 2	2/27	12±7.9	0
10	Crocid 3	15/23	93±6.9	5.01	46	Wollaston 2	2/25	12±8.0	0
11	Amosite	14/25	93±7.1	3.53	47	Crocid 12	2/27	10±7.0	3.73
12	Crocid 4	15/24	86±9.0	5.13	48	Attapul 2	2/29	11±7.5	0
13	Glass 1	9/17	85±13.2	5.16	49	Glass 10	2/27	8±5.6	0
14	Crocid 5	14/29	78±10.8	3.29	50	Glass 11	1/27	8±5.5	0
15	Glass 2	12/31	77±16.6	4.29	51	Titanate 3	1/28	8±8.0	0
16	Glass 3	20/29	74±8.5	3.59	52	Attapul 1	2/29	8±5.3	0
17	Glass 4	18/29	71±9.1	4.02	53	Talc 1	1/26	7±6.9	0
18	Alumin 1	15/24	70±10.2	3.63	54	Glass 12	1/25	7±5.4	0
19	Glass 5	16/25	69±9.6	3.00	55	Glass 13	1/27	6±5.7	0
20	Dawson 7	16/30	68±9.8	4.71	56	Glass 14	1/25	6±5.5	0
21	Dawson 4	11/26	66±12.2	4.01	57	Glass 15	1/24	6±5.9	1.30
22	Dawson 3	9/24	66±13.4	5.73	58	Alumin 7	1/25	5±5.1	0
23	Glass 6	7/22	64±17.7	4.01	59	Glass 16	1/29	5±4.4	0
24	Crocid 6	9/27	63±13.9	4.60	60	Talc 3	1/29	4±4.3	0
25	Crocid 7	11/26	56±11.7	2.65	61	Talc 2	1/30	4±3.8	0
26	Crocid 8	8/25	53±12.9	0	62	Talc 4	1/29	5±4.9	0
27	Alumin 2	8/27	44±11.7	2.95	63	Alumin 8	1/28	3±3.4	0
28	Alumin 3	9/27	41±10.5	2.47	64	Glass 21	2/47	6±4.4	0
29	Crocid 9	8/27	33±9.8	4.25	65	Glass 22	1/45	2±2.3	0
30	Wollaston 1	5/20	31±12.5	0	66	Glass 17	0/28	0	0
31	Alumin 4	4/25	28±12.0	2.60	67	Glass 18	0/115	0	0
32	Crocid 10	6/29	37±13.5	3.09	68	Crocid 13	0/29	0	0
33	Alumin 5	4/22	22±9.8	3.73	69	Wollaston 4	0/24	0	0
34	Glass 20	4/25	22±10.0	0	70	Talc 5	0/30	0	0
35	Glass 7	5/28	21±8.7	2.50	71	Talc 6	0/30	0	3.30
36	Wollaston 3	3/21	19±10.5	0	72	Talc 7	0/29	0	0

SD = Standard deviation.

Source: Stanton et al. (1981).

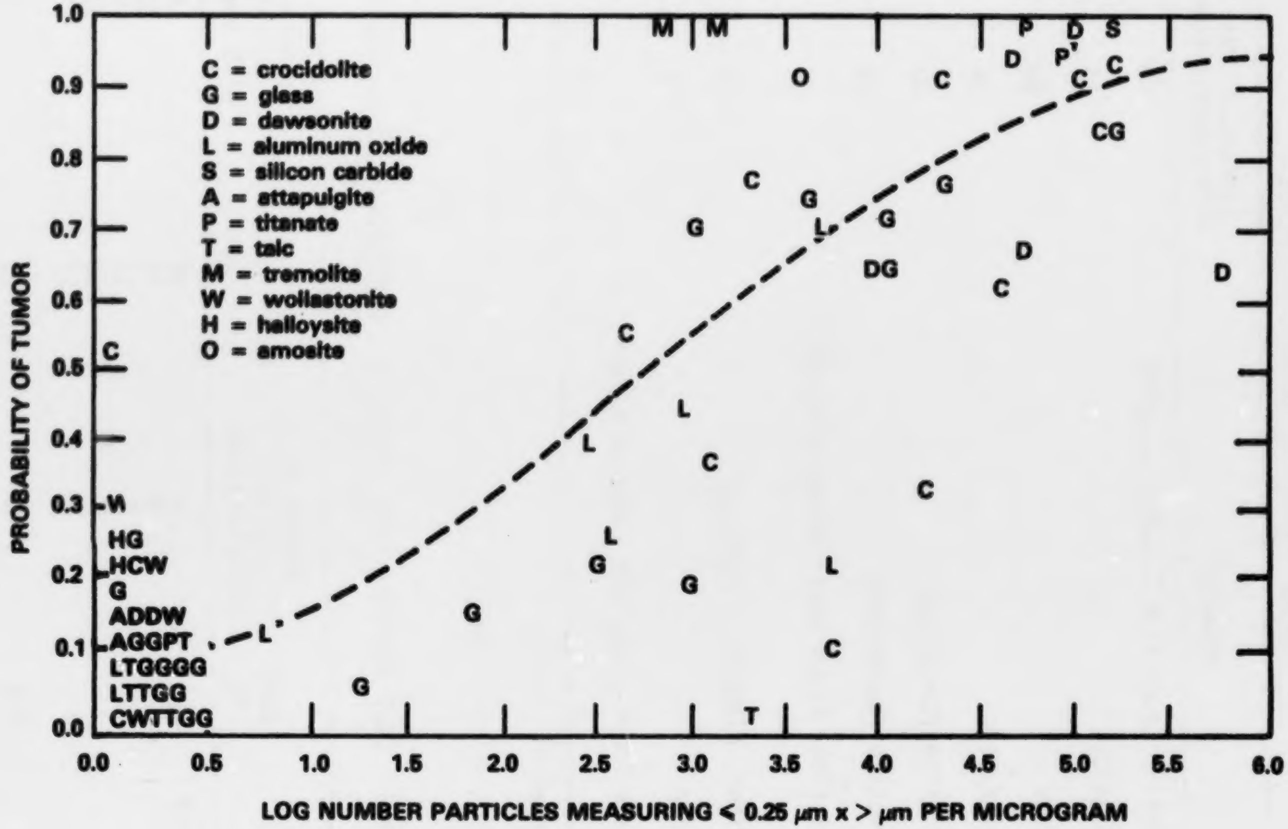


Figure 4-4. Regression curve relating probability of tumor to logarithm of number of particles per μg with diameter < 0.25 μm and length >8 μm.

Source: Stanton et al. (1981).

TABLE 4-8. PERCENTAGE OF RATS DEVELOPING MESOTHELIOMAS AFTER INTRAPLEURAL ADMINISTRATION OF VARIOUS MATERIALS

Material	Percent of rats with mesotheliomas
SFA chrysotile (superfine Canadian sample)	66
UICC crocidolite	61
UICC amosite	36
UICC anthophyllite	34
UICC chrysotile (Canadian)	30
UICC chrysotile (Rhodesian)	19
Fine glass fiber (code 100), median diameter = 0.12 μm	12
Ceramic fiber, diameter = 0.5-1 μm[a]	10
Glass powder	3
Coarse glass fiber (code 110), median diameter = 1.8 μm	0

[a] From Wagner et al. (1973).

Source: Wagner et al. (1976).

TABLE 4-9. DOSE-RESPONSE DATA FOLLOWING INTRAPLEURAL ADMINISTRATION OF ASBESTOS TO RATS

Material	Dose mg	Number of rats with mesothelioma	Total number of rats	Percent of rats with tumors
SFA chrysotile	0.5	1	12	8
	1	3	11	27
	2	5	12	42
	4	4	12	33
	8	8	12	62
Crocidolite	0.5	1	11	9
	1	0	12	0
	2	3	12	25
	4	2	13	15
	8	5	11	45

Source: Wagner et al. (1973).

4.7 INTRATRACHEAL INJECTION

Intratracheal injection has been used to study the combined effect of the administration of chrysotile with benzo(a)pyrene in rats and hamsters. No lung tumors were observed in rats given 3 doses of 2 mg of chrysotile (Shabad et al., 1974) and in hamsters given 12 mg of chrysotile (Smith et al., 1970). However, co-administration of benzo(a)pyrene resulted in lung tumors, which suggests a co-carcinogenic or synergistic effect.

4.8 INTRAPERITONEAL ADMINISTRATION

Intraperitoneal injections of 20 mg of crocidolite or chrysotile produced 3 peritoneal mesotheliomas in 13 Charles River CD rats, but 20 mg of amosite produced no tumors in a group of 11 rats (Maltoni and Annoscia, 1974). Maltoni and Annoscia also injected 25 mg of crocidolite into 50 male and 50 female 17-week-old Sprague-Dawley rats and observed 31 mesothelial tumors in males and 34 in females.

In an extensive series of experiments, Pott and Friedrichs (1972) and Pott et al. (1976) produced peritoneal mesotheliomas in mice and rats that were injected with various commercial varieties of asbestos and other fibrous material. These results are shown in Table 4-10. Using experiments with intrapleural administration, the malignant response was altered by ball-milling the fibers for 4 hours. The rate of tumor production was reduced from 55 to 32 percent and the time from onset of exposure to the first tumor was lengthened from 323 to 400 days following administration of 4 doses of 25 mg of UICC Rhodesian chrysotile. In the case of the ball-milled fibers, 99 percent of the fibers were reported to be smaller than 3 μm, 93 percent were smaller than 1 μm, and 60 percent were smaller than 0.3 μm.

Pott (1980) proposed a model for the relative carcinogenicity of mineral fibers, according to their dimensionality, using the results of injection and implantation data. Figure 4-5 shows the schematic features of this model. The greatest carcinogenicity is attributed to fiber lengths between 5 and 40 μm with diameters between 0.05 and 1 μm.

A strong conclusion that can be drawn from the above experimental data is that long (>4 μm) and fine diameter (<1 μm) fibers are more carcinogenic than short, thick fibers when they are implanted on the pleura or injected into the peritoneum of animals. The origin of a reduction in carcinogenicity for

TABLE 4-10. TUMORS IN ABDOMEN AND/OR THORAX OF RATS AFTER INTRAPERITONEAL INJECTION OF GLASS FIBERS, CROCIDOLITE, OR CORUNDUM

Dust	Form[a]	Intraperitoneal dose mg	Effective number of dissected rats	Number of days before first tumor	Average survival time of rats with tumors, days after injection	Rats with tumors, percent	Tumor/type[b]					
							1	2	3	4	5	6
Glass fibers MN 104	f	2	73	421	703	27.4	17	3	-	-	1	1
Glass fibers MN 104	f	10	77	210	632	53.2	36	4	-	1	3	-
Glass fibers MN 104	f	2 x 25	77	194	367	71.4	47	6	2	-	-	-
Crocidolite	f	2	39	452	761	38.5	12	3	-	-	2	1
Corundum	g	2 x 25	37	545	799	8.1	1	-	-	2	2	2
UICC Rhodesian chrysotile	f	2	37	431	651	16.2	4	2	-	-	1	-
UICC Rhodesian chrysotile	f	6.25	35	343	501	77.1	24	3	-	-	-	-
UICC Rhodesian chrysotile	f	25	31	276	419	0.6	21	2	1	1	-	-
UICC Rhodesian chrysotile	f	4 x 25	33	323	361	54.5	16	2	-	-	-	-
UICC Rhodesian chrysotile	f	3 x 25 s.c.	33	449	449	3.0	-	-	1 s.c.	-	-	-
UICC Rhodesian milled	f	4 x 25	37	400	509	32.4	9	3	-	-	-	-
Palygoescite	f	3 x 25	34	257	348	76.5	24	2	-	-	-	-

TABLE 4-10. (continued)

Dust	Form[a]	Intraperitoneal dose mg	Effective number of dissected rats	Number of days before first tumor	Average survival time of rats with tumors, days after injection	Rats with tumors, percent	Tumor/type[b]					
							1	2	3	4	5	6
Glass fibers S + S 106	f	2	34	692	692	2.9	1	-	-	-	-	-
Glass fibers S + S 106	f	10	36	350	530	11.1	2	2	-	-	1	-
Glass fibers S + S 106	f	4 x 25	32	197	325	71.9	20	3	-	-	-	-
Gypsum	f	4 x 25	35	579	583	5.7	-	-	1	1	1	-
Henalite	f	4 x 25	34	249	315	73.5	17	8	-	-	-	-
Actinolite	g	4 x 25	39	-	-	-	-	-	-	-	-	-
Biotite	g	4 x 25	37	-	-	-	-	-	-	-	-	-
Haematite (precipitation)	g	4 x 25	34	-	-	-	-	-	-	-	-	-
Haematite (mineral)	g	4 x 25	38	-	-	-	-	-	-	-	-	-
Pectolite	g	4 x 25	40	569	569	2.5	-	-	-	1	1	1
Sanidine	g	4 x 25	39	579	579	2.6	-	1	-	-	-	-
Talc	g	4 x 25	36	587	587	2.8	1	-	-	-	-	-
NaCl (control)	-	4 x 2 ml	72	-	-	-	-	-	-	-	-	-

[a] f = fibrous; g = granular.

[b] Tumor Types are: 1 Mesothelioma; 2 Spindle cell sarcoma; 3 Polym-cell sarcoma; 4 Carcinoma; 5 Reticulum cell sarcoma; 6 Benign -- not evaluated in tumor rates.

Sources: Pott and Friedrichs (1972); Pott et al. (1976).

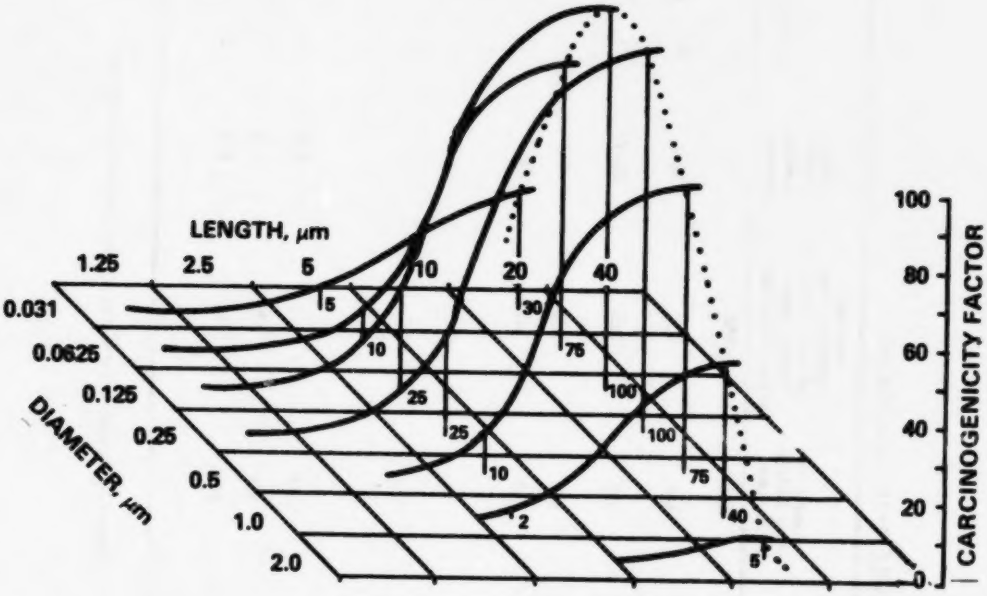


Figure 4-5. Hypothesis concerning the carcinogenic potency of a fiber as a function of its length and width using data on tumor incidence from injection and implantation studies.

Source: Pott (1980).

shorter, ball-milled fibers is less clear because the relative contributions of shorter fiber length and the significant alteration of the crystal structure by input of physical energy have not yet been defined. Extrapolation of data on size-dependent effects obtained from intrapleural or intraperitoneal administration, to inhalation, where movement of the fibers in airways and subsequently through body tissues is strongly size-dependent, presents significant difficulties. The number of shorter (<5 μm) fibers in an exposure circumstance may be 100 times greater than the number of longer fibers; therefore, their carcinogenicity must be 1/100 times as much before their contribution can be neglected.

4.9 TERATOGENICITY

There is no evidence that asbestos is teratogenic. Schneider and Maurer (1977) fed pregnant CD-1 mice doses of 4-400 mg/kg body weight (1.43 to 143) for gestation days 1 to 15. They also administered 1, 10, or 100 μg of asbestos to 4-day blastocysts, which were transferred to pseudopregnant mice. No positive effects were noted in either experiment.

4.10 SUMMARY

Animal data on the carcinogenicity of asbestos fibers confirm and extend epidemiological human data. Mesothelioma and lung cancer are produced by all the principal commercial asbestos varieties, chrysotile, amosite, crocidolite, and anthophyllite, even by exposures as short as one day. The deposition and clearance of fibers from the lung suggest that most inhaled fibers (~99 percent) are eventually cleared from the lung by ciliary or phagocytic action. Chrysotile appears to be more readily removed, and dissolution of the fibers occurs in addition to other clearance processes. Implantation and injection studies suggest that the carcinogenicity of durable mineral fibers is related to their dimensionality and not to their chemical composition. Long (≥4 μm) and thin (≤1 μm) fibers are most carcinogenic when they are in place at a potential tumor site. However, deposition, clearance, and migration of fibers are also size dependent, and the importance of all size-dependent effects in the carcinogenicity of inhaled fibers is not fully established.

5. ENVIRONMENTAL EXPOSURES TO ASBESTOS

5.1 INTRODUCTION

The analysis of ambient air samples for asbestos has utilized techniques different from those used in occupational circumstances. This situation occurred because typical urban air may contain up to 100 $\mu g/m^3$ of particulate matter in which the researcher is attempting to quantify asbestos concentrations from about 0.1 ng/m^3 to perhaps 1000 ng/m^3. Thus, asbestos may constitute only 0.0001 to 1 percent of the particulate matter in a given air sample. Asbestos found in ambient air has a size distribution such that the vast majority of fibers are too short or too thin to be seen with an optical microscope. In many cases, these fibers and fibrils will be agglomerated with a variety of other materials present in the air samples.

The only effective method of analysis uses electron microscopy to enumerate and size all asbestos fibers (Nicholson and Pundsack, 1973; Samudra et al., 1978). Samples for such analysis are usually collected either on a Nuclepore® (polycarbonate) filter with a pore size of 0.4 µm or on a Millipore® (cellulose ester) filter with a pore size of 0.8 µm. In some cases the Millipore® is backed by nylon mesh. Samples collected on Nuclepore® filters are prepared for direct analysis by carbon coating the filter to entrap the collected particles. A segment of the coated filter is then mounted on an electron microscope grid, which is placed on a filter paper saturated with chloroform so that the chloroform vapors dissolve the filter material. (Earlier electron microscopic analysis utilized a rub-out technique in which the ash residue was dispersed in a nitrocellulose film on a microscope slide and a portion of the film was then mounted on an electron microscope grid for scanning.)

Samples collected on Millipore® filters are prepared for indirect analysis by ashing a portion of the filter in a low temperature oxygen furnace. This removes the membrane filter material and all organic material collected in the sample. The residue is recovered in a liquid phase, dispersed by ultrasonification, and filtered on a Nuclepore® filter. The refiltered material is coated with carbon and mounted on a grid as above. The samples are then subjected to analysis. Chrysotile asbestos is identified on the basis of its morphology in the electron microscope and amphiboles are identified by their selected area electron diffraction patterns, supplemented by energy-dispersive X-ray analysis. Fiber concentrations in fibers per unit of volume (such as fibers/cm^3, fibers/m^3, etc.) are calculated based on sample volume and filter area counted. In some cases, mass concentrations are reported using fiber volume and density relationships. However, mass concentrations may not be reliable if the sample contains fibrous forms, such as clusters, bundles, and matrices, where fiber volume is difficult to determine. These materials may constitute most of the asbestos mass in some samples, particularly those reflecting emission sources. Current fiber counting methods do not include those clumps. However, many of them are respirable and to the extent that they are broken apart in the lungs into individual fibers, they may add to the carcinogenic risk. On the other hand, methods which break up fibers generally disperse the clumps as well. In such analyses, the clumps would contribute to the mass.

In much of the earlier analyses of chrysotile concentrations in the United States the ashed material was either physically dispersed or disrupted by ultrasonification. Thus, no information was obtained on the size distribution of the fibers in the original aerosol. Air concentrations were given only in terms of total mass of asbestos present in a given air volume, usually in nanograms per cubic meter (ng/m^3). (See Section 5-9 for data on the interconvertability of optical fiber counts and electron microscopic mass determinations.) With the use of Nuclepore® filters and appropriate care in the collection of samples and their processing, information on the fiber size distribution can be obtained and concentrations of fibers of selected dimensions can be calculated. Samples collected on Millipore® filters can be ashed and the residue resuspended and filtered through Nuclepore® filters. However, some breakage of fibers during the process is likely. Direct processing of Millipore® filters for electron microscopic analysis has been reported by Burdett and Rood (1983) and is being tested by several laboratories. However, the utility and reliability of this technique is unknown at present.

Ideally, one would like a measure of exposure that would be proportional to the carcinogenic risk. Unfortunately, this is not possible because of our limited information on the carcinogenicity of fibers according to length and width and the lack of information on the deposition, clearance, and movement through the body of fibers of different sizes. Secondly, our epidemiological evidence of disease relates to fibers longer than 5 μm measured by optical microscopy. It should be recognized that electron microscopic fiber counts of fibers longer than 5 μm of length will differ considerably from optical microscopy counts of the same sample because of the presence of a large number of fibers undetected by optical microscopy. Nevertheless, it would appear that the best measure of risk would be electron microscopic fiber counts of fibers greater than 5 µm in length and use of an empirically determined adjustment for the increased resolving power of the electron microscope when such measurements are used for risk assessment.

Two of the studies described below provide information on fiber as well as mass concentrations. However, in one case (Constant, 1983) the fiber concentrations were of fibers of all length, and thus are impossible to translate into optical microscopic counts (other than by mass). While the other studies are limited because of the absence of fiber concentrations, they are sufficient to indicate exposure circumstances of concern or that warrant further investigation. Further, using an empirical conversion factor (having a very large uncertainty), estimates of environmental exposures can be made in terms of optical fiber counts.

Unfortunately, few studies have been conducted which provide data relating asbestos fiber concentrations and health effects. While estimates of asbestos concentrations based on conversions from fiber-mass relationships have an associated uncertainty, they are the best data available for such assessments. Future studies will hopefully be designed to measure fiber number, size, and type for correlation with health effects.

An analysis of 25 samples collected in buildings having asbestos surfacing material (some buildings showing evidence of contamination) demonstrated the inadequacy of phase contrast optical microscopic techniques for the quantification of asbestos (Nicholson et al., 1975). Figure 5-1 shows the correlation of optical fiber counts determined using National Institute for Occupational Safety and Health (1972) prescribed techniques and asbestos mass measurements obtained on the same samples. In determining the fiber concentrations, all objects with an aspect ratio of three or greater were enumerated using phase-contrast microscopy. Petrographic techniques were not utilized to verify whether an object was an asbestos fiber. Figure 5-1 shows that the optical microscopic data do not reflect the mass concentrations of asbestos determined by electron microscopy, largely because of a considerable number of nonasbestos fibers that were in the ambient air and were counted in the optical microscopic analysis.

The available published asbestos exposure data are to a large extent episodic in nature. The studies were not designed to provide measures of ambient concentrations throughout the United States. The data presented here

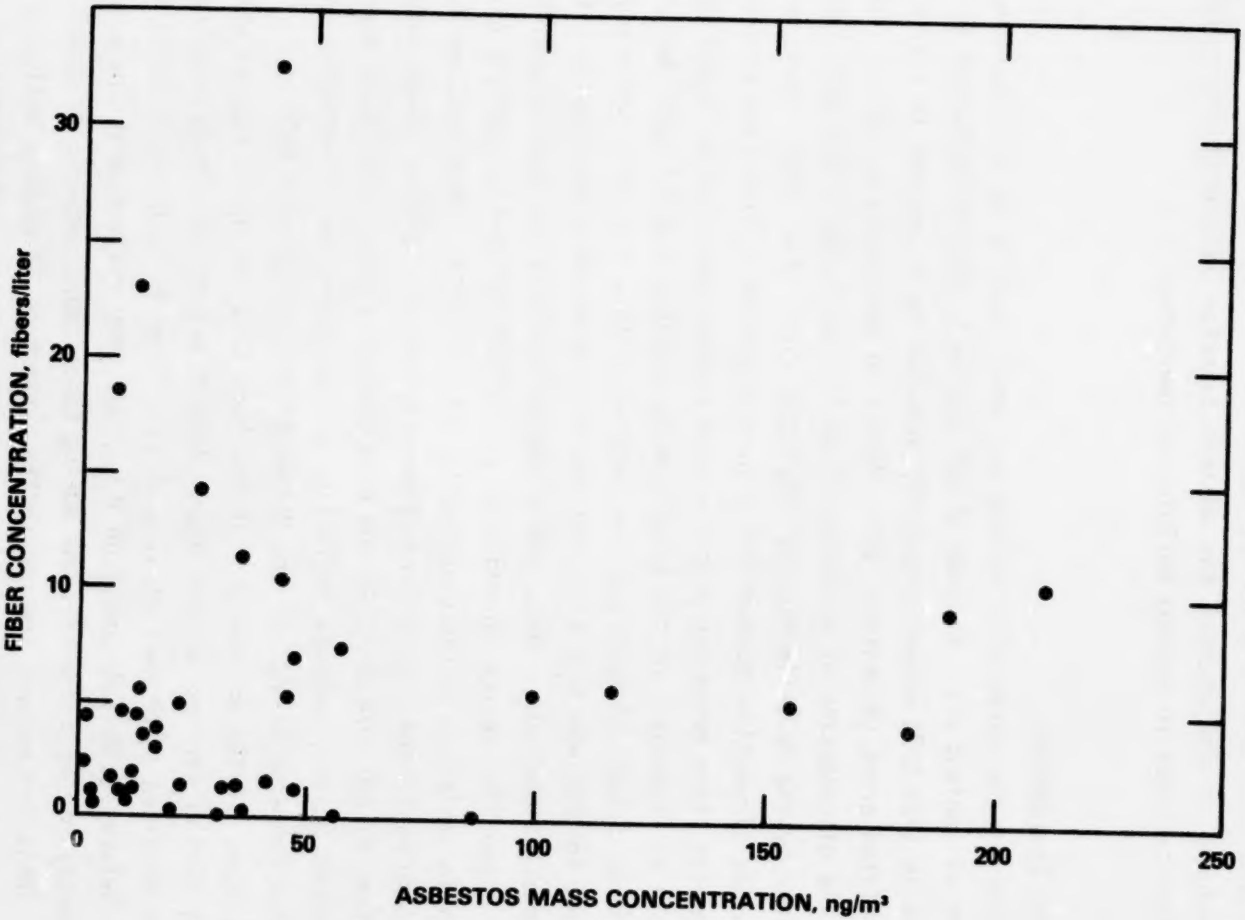


Figure 5-1. Fiber concentrations by optical microscopy versus asbestos mass concentrations by electron microscopy.

Source: National Institute for Occupational Safety and Health (1972).

represent the published data that are available. These data show what concentration can occur in the circumstances given. When useful information (i.e., number of sites, frequency of samples) is available that helps characterize the representativeness of exposure of the data, it is presented. But as can be seen, these data generally do not represent the results of systematic studies designed to characterize the ambient asbestos concentrations in the United States or those in typical building circumstances.

5.2 GENERAL ENVIRONMENT

Asbestos of the chrysotile variety has been found to be a ubiquitous contaminant of ambient air. A study of 187 quarterly samples collected in 48 U.S. cities in 1969-1970 showed chrysotile asbestos to be present in virtually all metropolitan areas (Nicholson, 1971; Nicholson and Pundsack, 1973). Table 5-1 lists the distribution of values obtained in that study, along with similar data obtained by the Battelle Memorial Institute (U.S. EPA, 1974). Each value represents the chrysotile concentration in a composite of from five to seven 24-hour samples, thus averaging possible peak concentrations which could occur periodically or randomly. Of the three samples greater than 20 ng/m^3 analyzed by Mount Sinai School of Medicine, one sample was in a city that had a major shipyard and another was in a city that had four brake manufacturing facilities with no emission controls. Thus, these samples may have included a contribution from a specific source in addition to that of the general ambient air. Also shown in Table 5-1 is the distribution of chrysotile concentrations from five-day samples of the air in Paris (Sebastien et al., 1980). These values were obtained during 1974 and 1975 and were generally lower than those measured in the United States, perhaps reflecting a diminished use of asbestos in construction compared to that of the United States during 1969-1970.

In a study of the ambient air of New York City, in which samples were taken only during daytime working hours, higher values than those mentioned above were obtained (Nicholson et al., 1971). These 4- to 8-hour samples were collected between 8:00 A.M. and 5:00 P.M., and they reflect what could be intermittently higher concentrations during those hours compared to nighttime periods. Table 5-2 records the chrysotile content of 22 samples collected in the five boroughs of New York and their overall cumulative distribution. The samples analyzed in all the studies discussed above were taken during a period when fireproofing of high rise buildings by spraying asbestos-containing

TABLE 5-1. CUMULATIVE DISTRIBUTION OF 24-HOUR CHRYSOTILE ASBESTOS CONCENTRATIONS IN THE AMBIENT AIR OF U.S. CITIES AND PARIS, FRANCE

	Electron Microscopy Analysis				
	Mount Sinai School of Medicine[a]		Battelle Memorial Institute[b]		Paris, France[c]
Concentration (ng/m^3) less than	Number of samples	Percentage of samples	Number of samples	Percentage of samples	Percentage of samples
1.0	61	32.6	27	21.3	70
2.0	119	63.6	60	47.2	85
5.0	164	87.7	102	80.1	98
10.0	176	94.2	124	97.6	100
20.0	184	98.5	125	98.5	
50.0	185	99.0	127	100.0	
100.0	187	100.0	127	100.0	

Sources: [a] [illegible] (1971); [b]U.S. EPA (1974); [c]Sebastien et al. (1980).

materials was permitted. The practice was especially common in New York City. While no sampling station was known to be located adjacent to an active construction site, unusually high levels could nevertheless have resulted from this procedure. Other sources that may have contributed to these air concentrations include automobile braking, other construction activities, consumer use of asbestos products, and maintenance or repair of asbestos-containing materials (e.g., thermal insulation).

5.3 CHRYSOTILE ASBESTOS CONCENTRATIONS NEAR CONSTRUCTION SITES

To determine if construction activities could be a significant source of chrysotile fiber in the ambient air, 6- to 8-hour daytime sampling was conducted in lower Manhattan in 1969 near sites where extensive spraying of asbestos-containing fireproofing material was taking place. Eight sampling sites were established near the World Trade Center construction site during the period when asbestos material was sprayed on the steelwork of the first tower.

TABLE 5-2. DISTRIBUTION OF 4- TO 8-HOUR DAYTIME CHRYSOTILE ASBESTOS CONCENTRATIONS IN THE AMBIENT AIR OF NEW YORK CITY, 1969-1970

Asbestos concentration (ng/m^3) less than	Cumulative number of samples	Cumulative percentage of samples
1	0	0.0
2	1	4.5
5	4	18.1
10	8	36.4
20	16	72.7
50	21	95.4
100	22	100.0

Distribution by borough

Sampling locations	Number of samples	Asbestos air level, ng/m^3 Range	Asbestos air level, ng/m^3 Average
Manhattan	7	8-65	30
Brooklyn	3	6-39	19
Bronx	4	2-25	12
Queens	4	3-18	9
Staten Island	4	5-14	8

Source: Nicholson et al. (1971).

Table 5-3 shows the results of building-top air samples taken at sites within one-half mile of the Trade Center site, demonstrating that spray fireproofing did contribute significantly to asbestos air pollution (Nicholson et al., 1971; Nicholson and Pundsack, 1973). In some instances, chrysotile asbestos levels were observed that were approximately 100 times greater than the concentrations typically found in ambient air.

5.4 ASBESTOS CONCENTRATIONS IN BUILDINGS IN THE UNITED STATES AND FRANCE

During 1974, 116 samples of indoor and outdoor air were collected in 19 buildings (usually 4-6 indoor samples and 1 ambient air control sample per building) in 5 U.S. cities to assess whether contamination of the building air resulted from the presence of asbestos-containing surfacing materials in rooms or return air plenums (Nicholson et al., 1975). The asbestos materials in the buildings were of two main types: 1) a cementitious or plaster-like material that had been sprayed as a slurry onto steelwork or building surfaces, and

TABLE 5-3. DISTRIBUTION OF 6- TO 8-HOUR CHRYSOTILE ASBESTOS CONCENTRATIONS WITHIN ONE-HALF MILE OF THE SPRAYING OF ASBESTOS MATERIALS ON BUILDING STEELWORK, 1969-1970

Asbestos concentration (ng/m^3) less than	Cumulative number of samples	Cumulative percentage of samples
5	0	0.0
10	3	17.6
20	8	47.1
50	14	82.3
100	16	94.1
200	16	94.1
500	17	100.0

Distribution of chrysotile air levels according to distance from spray fireproofing sites

Sampling locations	Number of samples	Asbestos air level, ng/m^3	
		Range	Average
1/8-1/4 mile	11	9-375	60
1/4-1/2 mile	6	8-54	25
1/2-1 mile	5	3.5-36	18

Source: Nicholson et al. (1971).

2) a loosely bonded fibrous mat that had been applied by blowing a dry mixture of fibers and binders through a water spray onto the desired surface. The friability of the two types of materials differed considerably; the cementitious spray surfaces were relatively impervious to damage while the fibrous sprays were highly friable. The results of air sampling in these buildings (Table 5-4) provide evidence that the air of buildings with fibrous asbestos-containing materials may often be contaminated.

Similar data were obtained by Sebastien et al. (1980) in a survey of asbestos concentration in buildings in Paris, France. Sebastien surveyed 21 asbestos-insulated buildings; 12 had at least one measurement higher than 7 ng/m^3, the upper limit of the outdoor asbestos concentrations measured by these investigators. The distribution of 5-day asbestos concentrations in these buildings, along with 19 outdoor samples taken at the same time, is shown in Table 5-5. One particularly disturbing set of data by Sebastien et al. is the concentrations of asbestos measured after surfacing material was removed or repaired. The average of 22 such samples was 22.3 ng/m^3. However,

TABLE 5-4. CUMULATIVE DISTRIBUTION OF 8- TO 16-HOUR CHRYSOTILE ASBESTOS CONCENTRATIONS IN BUILDINGS WITH ASBESTOS-CONTAINING SURFACING MATERIALS IN ROOMS OR IN AIR PLENUMS

Asbestos concentration ng/m^3 less than	Friable spray		Cementitious spray		Control samples	
	Number of samples	Percentage of samples	Number of samples	Percentage of samples	Number	Percentage
1	5	9.3	3	10.7	5	14.7
2	6	11.1	6	21.4	6	17.6
5	8	14.8	10	35.7	15	44.1
10	15	27.8	17	60.7	21	61.8
20	28	51.9	26	92.9	29	85.3
50	44	81.5	27	96.4	33	97.1
100	49	90.7	27	96.4	34	100.0
200	52	96.3	28	100.0		
500	53	98.1				
1000	54	100.0				
Arithmetic average concentration		48 ng/m^3		14.5 ng/m^3		12.7 ng/m^3

Source: Nicholson et al. (1975; 1976).

TABLE 5-5. CUMULATIVE DISTRIBUTION OF 5-DAY ASBESTOS CONCENTRATIONS IN PARIS BUILDINGS WITH ASBESTOS-CONTAINING SURFACING MATERIALS

Asbestos concentration (ng/m³) less than	Building samples		Outdoor control samples	
	Number	Percentage	Number	Percentage
Chrysotile				
1	57	42.2	14	73.7
2	70	51.9	16	84.2
5	92	68.1	17	89.5
10	104	77.0	19	100.0
20	117	86.7		
50	128	94.8		
100	129	95.6		
200	130	96.3		
500	132	97.8		
1000	135	100.0		
Arithmetic average concentration		25 ng/m³		1 ng/m³
Amphiboles[a]				
1	112	83.0	19	100.0
2	115	85.2		
5	122	90.4		
10	125	92.6		
20	129	95.6		
50	131	97.0		
100	132	97.8		
200	133	98.5		
500	135	100.0		
Arithmetic average concentration		10 ng/m³		0.1 ng/m³

[a] No value reported for 104 building samples. Some materials would have contained no amphibole asbestos.

Source: Sebastien et al. (1980).

in two highly contaminated areas, significant reductions were measured (500 to 750 ng/m^3 decreased to less than 1 ng/m^3). The importance of proper removal techniques and cleanup cannot be overemphasized.

Sebastien et al. (1982) also measured concentrations of indoor airborne asbestos up to 170 ng/m^3 in a building with weathered asbestos floor tiles. Asbestos flooring is used in a large number of buildings and is the third largest use of asbestos fibers.

5.5 ASBESTOS CONCENTRATIONS IN U.S. SCHOOL BUILDINGS

Of concern was the discovery of extensive asbestos use in public school buildings (Nicholson et al., 1978). Asbestos surfaces were found in more than 10 percent of pupil-use areas in New Jersey schools, with two-thirds of the surfaces showing some evidence of damage. Because these values appear to be typical of conditions in many other states, it was estimated that 2 to 6 million pupils and 100,000 to 300,000 teachers may be exposed to released asbestos fibers in schools across the nation. To obtain a measure of contamination for this use of asbestos, 10 schools were sampled in the urban centers of New York and New Jersey and in suburban areas of Massachusetts and New Jersey. Schools were selected for sampling because of visible damage, in some cases extensive.

Table 5-6 lists the distribution of chrysotile concentrations found in samples taken over 4 to 8 hours in these 10 schools (1-5 samples per school). Chrysotile asbestos concentrations ranged from 9 ng/m^3 to 1950 ng/m^3, with an average of 217 ng/m^3. Outside air samples at 3 of the schools varied from 3 ng/m^3 to 30 ng/m^3, with an average of 14 ng/m^3. In all samples but two (which measured 320 ng/m^3) no asbestos was visible on the floor of the sampled area, although surface damage was generally present near the area. The highest value (1950 ng/m^3) was in a sample that followed routine sweeping of a hallway in a school with water damage to the asbestos surface, although no visible asbestos was seen on the hallway floor. It is emphasized that the schools were selected in testing on the basis of the presence of visible damage. Although the results cannot be considered typical of all schools having asbestos surfaces, the results do illustrate the extent to which contamination can exist.

A recent study suggests that the above school samples may not be atypical (Constant et al., 1983). Concentrations similar to those indicated above were found in the analysis of samples collected during a 5-day period in 25

TABLE 5-6. DISTRIBUTION OF CHRYSOTILE ASBESTOS CONCENTRATIONS IN 4- to 8-HOUR SAMPLES TAKEN IN PUBLIC SCHOOLS WITH DAMAGED ASBESTOS SURFACES

Asbestos concentration (ng/m^3) less than	Number of samples	Percentage of samples
5	0	0.0
10	1	3.7
20	1	3.7
50	6	22.2
100	12	44.4
200	19	70.4
500	25	92.6
1000	26	96.3
2000	27	100.0

Source: Nicholson et al. (1978).

schools that had asbestos surfacing materials. The schools were in a single district and were selected by a random procedure, not because of the presence or absence of damaged material. A population-weighted arithmetic mean concentration of 179 ng/m^3 was measured in 54 samples collected in rooms or areas that had asbestos surfacing material. In contrast, a concentration of 6 ng/m^3 was measured in 31 samples of outdoor air taken at the same time. Of special concern are 31 samples collected in the schools that used asbestos, but taken in areas where asbestos was not used. These data showed an average concentration of 53 ng/m^3, indicating dispersal of asbestos from the source. The data are summarized in Table 5-7. As published fiber counts were fibers of all sizes, only the fiber mass data are listed in the table. Additionally, fiber clumps were noted in many samples, but were not included in the tabulated masses.

A study commissioned by the Ontario Royal Commission (1984) of asbestos concentrations in buildings with asbestos insulation indicates levels comparable to that of urban air. It is not clear whether "insulation" is thermal insulation or sprayed surfacing material. Average concentrations (3-5 samples per building) ranged from less than 1 to 11 ng/m^3. However, during very careful maintenance and inspection work, concentrations substantially in excess of background were observed.

Sawyer (1977, 1979) reviewed a variety of data on air concentrations, measured by optical microscopy, for circumstances where asbestos materials in schools and other buildings are disturbed by routine or abnormal activity.

TABLE 5-7. CUMULATIVE DISTRIBUTION OF 5-DAY CHRYSOTILE ASBESTOS CONCENTRATIONS IN 25 SCHOOLS HAVING ASBESTOS SURFACING MATERIALS, 1980-1981

Asbestos concentration (ng/m^3) less than	Rooms with asbestos		Rooms without asbestos		Outdoor controls	
	Number of samples	Percentage of samples	Number of samples	Percentage of samples	Number of samples	Percentage of samples
			Chrysotile			
1	5	9.2	6	19.4	17	54.8
2	6	11.1	7	22.6	22	71.0
5	7	13.0	11	35.5	27	87.1
10	14	25.9	12	38.7	28	90.3
20	19	35.2	15	48.4	30	96.8
50	26	48.1	21	67.7	31	100.0
100	39	72.2	24	87.1		
200	45	83.3	29	93.5		
500	52	96.3	31	100.0		
1000	54	100.0				
Population weighted mean concentration		179 ng/m^3		53 ng/m^3		6 ng/m^3
			Amphiboles			
1	44	81.5	21	67.7	26	83.9
2	45	83.3	22	71.0	29	93.5
5	49	90.7	26	83.9	31	100.0
10	50	92.6	27	87.1		
20	52	96.3	27	87.1		
50	52	96.3	29	93.5		
100	54	100.0	31	100.0		
500						
Arithmetic mean concentration		3.6 ng/m^3		8.3 ng/m^3		0.5 ng/m^3

Source: Constant et al. (1983).

These results, shown in Table 5-8, demonstrate that a wide variety of activities can lead to high asbestos concentrations during disturbance of asbestos surfacing material. Maintenance and renovation work, particularly if performed improperly, can lead to substantially elevated asbestos levels.

TABLE 5-8. AIRBORNE ASBESTOS IN BUILDINGS HAVING FRIABLE ASBESTOS MATERIALS

Classification	Main mode of contamination	Activity description	Mean count of fibers per cm^3	n	Range or SD
Quiet, non-specific, routine	Fallout reentrainment	None	0.0	32	0.0
		Dormitory	0.1	NA	0.0-0.8
		University, schools	0.1	47	0.1
		Offices	0.2	14	0.1-0.6
Maintenance	Contact	Relamping	1.4	2	0.1
		Plumbing	1.2	6	0.1-2.4
		Cable movement	0.9	4	0.2-3.2
Custodial	Mixed: contact reentrainment	Cleaning	15.5	3	6.7
		Dry sweeping	1.6	5	0.7
		Dry dusting	4.0	6	1.3
		Bystander	0.3	3	0.3
		Heavy dusting	2.8	8	1.6
Renovation	Mixed: contact reentrainment	Ceiling repair	17.7	3	8.2
		Track light	7.7	6	2.9
		Hanging light	1.1	5	0.8
		Partition	3.1	4	1.1
		Pipe lagging	4.1	8	1.8-5.8
Vandalism	Contact	Ceiling damage	12.8	5	8.0

Source: Sawyer (1979).

5.6 CHRYSOTILE CONCENTRATIONS IN THE HOMES OF WORKERS

The finding of asbestos disease in family contacts of individuals occupationally exposed to chrysotile fibers directs attention to air concentrations in the homes of such workers. Thirteen samples were collected in the homes of asbestos mine and mill employees and analyzed for chrysotile (Nicholson et al., 1980). The workers were employed at mine operations in California and Newfoundland. At the time of sampling (1973 and 1976) they did not have access to shower facilities nor did they commonly change clothes before going home. Table 5-9 lists the concentration ranges of the home samples. Three samples taken in homes of non-miners in Newfoundland yielded concentrations of 32, 45, and 65 ng/m^3. In contrast, the concentrations in workers' homes were much higher, pointing to the need for appropriate shower and change facilities at asbestos workplaces. Because asbestos-generated cancers have been documented in family contacts of workers, concentrations such as those described in this document should be viewed with particular concern.

TABLE 5-9. DISTRIBUTION OF 4-HOUR CHRYSOTILE ASBESTOS CONCENTRATIONS IN THE AIR OF HOMES OF ASBESTOS MINE AND MILL EMPLOYEES

Asbestos concentration (ng/m^3) less than	Number of samples	Percentage of samples
50	0	0.0
100	4	30.8
200	8	61.5
500	10	76.9
1000	12	92.3
2000	12	92.3
5000	13	100.0

Source: Nicholson et al. (1980).

5.7 SUMMARY OF ENVIRONMENTAL SAMPLING

Table 5-10 summarizes those studies of the general ambient air or of specific pollution circumstances that have a sufficient number of samples for comparative analysis. The data are remarkably consistent. Average 24-hour samples of general ambient air indicate asbestos concentrations of 1 to 2 ng/m^3 (two U.S. samples that may have been affected by specific sources were not included). Short-term daytime samples are generally higher, reflecting the possible contributions of traffic, construction, and other human activities. In buildings having asbestos surfacing materials, average concentrations 100 times greater than ambient air are seen in some schools and concentrations 5-30 times greater than ambient air are seen in some other buildings.

Figure 5-2 shows the cumulative distributions, on a log-probability plot, of the urban, school, and building samples. The straight lines in the data of Nicholson are suggestive of homogeneous sampling circumstances, but this may be fortuitous. The sampling situation of Constant et al. appears not to be homogeneous.

TABLE 5-10. SUMMARY OF ENVIRONMENTAL ASBESTOS SAMPLING

Sample set	Collection period	Number of samples	Mean Concentration, ng/m^3
Quarterly composites of 5 to 7 24-hour U.S. samples (Nicholson, 1971; Nicholson and Pundsack, 1973)	1969-70	187	3.3 C[a]
Quarterly composite of 5 to 7 24-hour U.S. samples (U.S. EPA, 1974)	1969-70	127	3.4C
5-day samples of Paris, France (Sebastien et al., 1980)	1974-75	161	0.96 C
6- to 8-hour samples of New York City (Nicholson et al., 1971)	1969	22	16 C
5-day, 7-hour control samples for U.S. school study (Constant et al., 1983)	1980-81	31	6.5 (6C, 0.5A[b])
16-hour samples of 5 U.S. cites (U.S. EPA, 1974)	1974	34	13 C
New Jersey schools with damaged asbestos surfacing materials in pupil use areas (Nicholson et al., 1978)	1977	27	217 C
U.S. school rooms/areas with asbestos surfacing material (Constant, 1983)	1980-81	54	183 (179C, 4A)
U.S. school rooms/areas in building with asbestos surfacing material (Constant, 1983)	1980-81	31	61 (53C, 8A)
Buildings with asbestos materials in Paris, France (Sebastien et al., 1980)	1976-77	135	35 (25C, 10A)
U.S. buildings with friable asbestos in plenums or as surfacing materials (Nicholson et al., 1975; Nicholson et al., 1976)	1974	54	48 C
U.S. buildings with cementitious asbestos material in plenums or as surfacing materials (Nicholson et al., 1975, 1976)	1974	28	15 C
Ontario buildings with asbestos insulation (Ontario Royal Commission, 1984)	1982	63	2.1

[a] C = chrysotile. [b] A = amphibole.

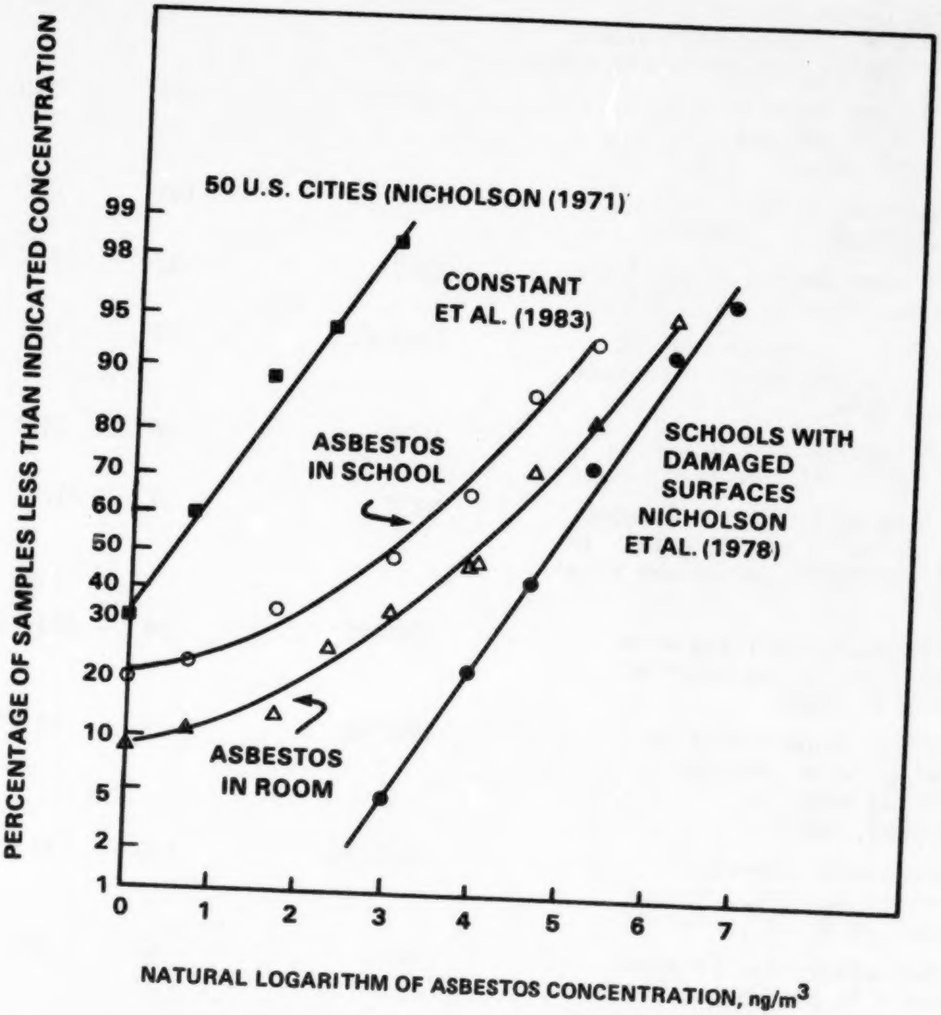


Figure 5-2. Cumulative distribution, on a log probability plot, of urban, school, and building asbestos air concentrations.

5.8 OTHER EMISSION SOURCES

Weathering of asbestos cement wall and roofing materials was shown to be a source of asbestos air pollution by analyzing air samples taken in buildings constructed of such material (Nicholson, 1978). Seven samples taken in a school after a heavy rainfall showed asbestos concentrations from 20-4500 ng/m^3 (arithmetic mean = 780 ng/m^3); all but two samples exceeded 100 ng/m^3. The source was attributed to asbestos washed from asbestos cement walkways and asbestos cement roof panels. No significantly elevated concentrations were observed in a concurrent study of houses constructed of asbestos cement materials. Roof water runoff from the homes landed on the ground and was not reentrained, while that of the schools fell to a smooth walkway, which allowed easy reentrainment when dry. Contamination from asbestos cement siding has also been documented by Spurny et al. (1980).

One of the more significant remaining contributions to environmental asbestos concentrations may be emissions from braking of automobiles and other vehicles. Measurements of brake and clutch emissions reveal that, annually, 2.5 tons of unaltered asbestos are released to the atmosphere and an additional 68 tons fall to roadways, where some of the asbestos is dispersed by passing traffic (Jacko et al., 1973).

5.9 INTERCONVERTIBILITY OF FIBER AND MASS CONCENTRATIONS

The limited data that relate asbestos disease to exposure are derived from studies of workers exposed in occupational environments. In these studies, concentrations of fibers longer than 5 µm were determined using optical microscopy or they were estimated from optical microscopy measurements of total particulate matter. All current measurements of low-level environmental pollution utilize electron microscopy techniques, which determine the total mass of asbestos present in a given volume of air. In order to extrapolate dose-response data obtained in studies of working groups to environmental exposures, it is necessary to establish a relationship between optical fiber counts and the mass of asbestos determined by electron microscopy.

Data are available relating optical fiber counts (longer than 5 µm) to the total mass of asbestos, as determined by electron microscopy techniques or other weight determinations. These relationships (Table 5-11) provide crude

TABLE 5-11. MEASURED RELATIONSHIPS BETWEEN OPTICAL FIBER COUNTS AND MASS AIRBORNE CHRYSOTILE

Sampling situation	Fiber[a] counts f/ml	Mass concentration μg/m³	Conversion factors	
			$\frac{\mu g/m^3}{f/ml}$ or $\frac{\mu g}{10^6 f}$	10^3 f/μg
Textile factory British Occupational Hygiene Society (1968) (weight vs. fiber count)	2	120	60	16
Air chamber monitoring Davis et al. (1978)	1950	10,000	5	200
Monitoring brake repair work Rohl et al. (1976) Electron Microscopy (E.M. mass vs. fiber count)	0.1 to 4.7 (7 samples)	0.1 to 6.6	0.7 to 24[b] mean = 6	170
Textile mill Lynch et al. (1970)			150[c]	6.7
Friction products manufacturing Lynch et al. (1970)			70[c]	13.9
Pipe manufacturing Lynch et al. (1970)			45[c]	22.5

[a] All fiber counts used phase-contrast microscopy and enumerated fibers longer than 5 μm.

[b] Conversion factor may be low due to losses in electron microscopy processing.

[c] Conversion factor may be high because of overestimate of asbestos mass on the basis of total magnesium.

estimates of a conversion factor relating fiber concentration in fibers per milliliter (f/ml) to airborne asbestos mass in micrograms per cubic meter ($\mu g/m^3$). The proposed standards for asbestos in Great Britain, set by the British Occupational Hygiene Society (BOHS), states that a "respirable" asbestos mass of 0.12 mg/m^3 is equivalent to 2 f/ml (British Occupational Hygiene Society, 1968). The standard does not state how this relationship was determined. If the relationship was obtained from magnesium determinations in an aerosol, the weight determination would likely be high because of the presence of other nonfibrous magnesium-containing compounds in the aerosol. Such was the case in the work of Lynch et al. (1970), and their values for the conversion factor are undoubtedly overestimates. The data of Rohl et al. (1976) are likely to be underestimates because of possible losses in the determination of mass by electron microscopy. No information exists on the procedures used to determine the mass of chrysotile in the data presented by Davis et al. (1978).

The range of 5 to 150 for the conversion factor relating mass concentration to optical fiber concentration is large and any average value derived from it has a large uncertainty. However, for the purpose of extrapolating to low mass concentrations from fiber count, the geometric mean of the above range of conversion factors, 30 $\mu g/m^3/f/ml$, will be used. The geometric standard deviation of this value is 4, and this uncertainty severely limits any extrapolation in which it is used. In the case of amosite, the data of Davis et al. (1978) suggest that a conversion factor of 18 is appropriate. However, these data yield lower chrysotile values than all other chrysotile estimates; therefore, they may also be low for amosite.

5.10 SUMMARY

Measurements using electron microscopy techniques established the presence of asbestos in the urban ambient air, usually at concentrations less than 10 ng/m^3. Concentrations of 100 ng/m^3 to 1000 ng/m^3 were measured near specific asbestos emission sources, in schools where asbestos-containing materials are used for sound control, and in office buildings where similar materials are used for fire control. Excess concentrations in buildings have usually been associated with visible damage or erosion of the asbestos materials. Many buildings with intact material have no increased concentrations of asbestos. Most ambient measurements were taken over ten years ago and it is very important to obtain more current data.

6. RISK EXTRAPOLATIONS AND HUMAN EFFECTS OF LOW EXPOSURES

6.1 RISK EXTRAPOLATIONS FOR LUNG CANCER AND MESOTHELIOMA

To obtain dose-response estimates at current or projected environmental asbestos concentrations, it is necessary to extrapolate from epidemiological data on deaths that have resulted from exposures to the considerably higher concentrations extant in occupational circumstances. As mentioned previously, the available data are compatible with a linear exposure-response relationship, with no evidence of a threshold. However, the limited data that indicate the validity of this relationship are for exposures two or three orders of magnitude higher than those of concern for environmental exposures.

The values determined for K_L and K_M in Chapter 3 are used to calculate best estimate risks from continuous exposures to 0.0001 and 0.01 f/ml. The values for continuous exposure were derived by multiplying 40 hr/wk risks, obtained from occupational exposures, by 4.2 (the ratio of hours in a week to 40 hours.) The lower concentration is typical of urban ambient air and corresponds to about 3 ng/m^3. The higher concentration, corresponding to about 300 ng/m^3, was measured in several environmental exposure circumstances. These two examples provide unit risks from which risk at other continuous exposures can be calculated as needed.

Tables 6-1, 6-2, and 6-3 list the calculated lifetime risks of mesothelioma and lung cancer for continuous exposures to 0.0001 and 0.01 f/ml of asbestos for various time periods. Risks from longer or shorter exposures can be estimated by directly scaling the data in the tables, as can risks from other concentrations (i.e., 0.1 f/ml). Equations 3-3a, 3-6c, 3-6d, and 3-6e and values of $K_L = 1.0 \times 10^{-2}$ and $K_M = 1.0 \times 10^{-8}$ were used in these calculations. The calculation uses a lifetable approach, in which the hypothetical population at risk is continuously decreased by its calculated mortality from all causes. Different overall mortality rates for smokers and non-smokers, as well as for males and females, lead to different estimated mesothelioma risks by smoking and gender, in Tables 6-1, 6-2, and 6-3. In the calculation of lung cancer risk it was assumed that the calculated asbestos-related risk continue following cessation of any hypothetical exposure. U.S. 1977 mortality rates (National Center for Health Statistics, 1977) are used as the basic data for the calculation. The tables utilize both smoking specific (Tables 6-1 and

TABLE 6-1. LIFETIME RISKS PER 100,000 FEMALES OF DEATH FROM MESOTHELIOMA AND LUNG CANCER FROM CONTINUOUS ASBESTOS EXPOSURES OF 0.0001 AND 0.01 f/ml ACCORDING TO AGE AT FIRST EXPOSURE, DURATION OF EXPOSURE, AND SMOKING[a]

Age at onset of exposure	Concentration = 0.0001 f/ml years of exposure -					Concentration = 0.01 f/ml years of exposure				
	1	5	10	20	lifetime	1	5	10	20	lifetime
Mesothelioma in Female Smokers										
0	0.1	0.6	1.2	1.9	2.5	13.9	64.0	115.1	186.2	252.0
10	0.1	0.4	0.7	1.1	1.4	9.0	40.3	71.4	112.0	142.8
20	0.1	0.2	0.4	0.6	0.7	5.3	23.5	40.7	61.3	72.8
30	0.0	0.1	0.2	0.3	0.3	2.8	12.3	20.6	29.4	32.8
50	0.0	0.0	0.0	0.0	0.0	0.6	2.0	2.9	3.5	3.5
Lung Cancer in Female Smokers										
0	0.0	0.1	0.3	0.5	1.5	2.8	13.4	26.7	53.3	149.9
10	0.0	0.1	0.3	0.5	1.2	2.8	13.4	26.7	53.3	123.5
20	0.0	0.1	0.3	0.5	1.0	2.8	13.4	26.7	52.5	96.9
30	0.0	0.1	0.3	0.5	0.7	2.8	13.3	25.9	47.9	71.0
50	0.0	0.1	0.2	0.2	0.2	2.0	8.8	15.5	22.7	24.4
Mesothelioma in Female Nonsmokers										
0	0.1	0.7	1.2	2.0	2.7	14.8	68.2	122.8	199.4	272.2
10	0.1	0.4	0.8	1.2	1.6	9.5	43.4	81.2	121.2	155.8
20	0.1	0.3	0.4	0.7	0.8	5.7	25.6	44.4	67.2	80.6
30	0.0	0.1	0.2	0.3	0.4	3.1	13.6	23.0	32.9	36.8
50	0.0	0.0	0.0	0.0	0.0	0.6	2.2	3.4	4.1	4.1
Lung Cancer in Female Nonsmokers										
0	0.0	0.0	0.0	0.1	0.2	0.3	1.3	2.7	5.2	16.4
10	0.0	0.0	0.0	0.1	0.1	0.3	1.3	2.7	5.3	13.9
20	0.0	0.0	0.0	0.1	0.1	0.3	1.3	2.7	5.2	11.3
30	0.0	0.0	0.0	0.1	0.1	0.3	1.3	2.7	5.0	8.7
50	0.0	0.0	0.0	0.0	0.0	0.3	1.1	2.1	3.5	3.9

[a] The 95% confidence limit on the risk values for lung cancer for an unstudied exposure circumstance is a factor of 10. The 95% confidence limit on the risk values for lung cancer on the average determined from 11 unit exposure risk studies is a factor of 2.5. The 95% confidence limit on the risk values for mesothelioma for an unstudied exposure circumstance is a factor of 20. The 95% confidence limit on the risk values for mesothelioma for a studied circumstance can be reasonably averaged as a factor of 5. The values for continuous exposure were derived by multiplying 40 hr/wk risks, obtained from occupational exposures, by 4.2 (the ratio of hours in a week to 40 hours.)

TABLE 6-2. LIFETIME RISKS PER 100,000 MALES OF DEATH FROM MESOTHELIOMA AND LUNG CANCER FROM CONTINUOUS ASBESTOS EXPOSURES OF 0.0001 AND 0.01 f/ml ACCORDING TO AGE AT FIRST EXPOSURE, DURATION OF EXPOSURE, AND SMOKING[a]

	Concentration = 0.0001 f/ml years of exposure					Concentration = 0.01 f/ml years of exposure				
Age at onset of exposure	1	5	10	20	lifetime	1	5	10	20	lifetime
					Mesothelioma in Male Smokers					
0	0.1	0.5	0.9	1.4	1.8	10.6	48.3	85.5	137.5	181.0
10	0.1	0.3	0.5	0.8	1.0	6.6	29.4	51.5	77.8	98.3
20	0.0	0.2	0.3	0.4	0.5	3.6	16.4	28.0	41.2	47.9
30	0.0	0.1	0.1	0.1	0.2	2.0	8.1	13.4	18.5	20.2
50	0.0	0.0	0.0	0.0	0.0	0.3	1.1	1.5	1.8	1.8
					Lung Cancer in Male Smokers					
0	0.0	0.2	0.4	0.8	2.4	4.2	20.9	41.9	83.4	238.1
10	0.0	0.2	0.4	0.8	2.0	4.2	21.0	42.0	83.9	197.8
20	0.0	0.2	0.4	0.8	1.6	4.2	21.3	42.3	83.4	157.5
30	0.0	0.2	0.4	0.8	1.2	4.2	21.3	42.0	79.2	117.6
50	0.0	0.2	0.3	0.4	0.4	3.6	16.2	28.4	40.3	42.0
					Mesothelioma in Male Nonsmokers					
0	0.1	0.6	1.0	1.6	2.2	12.5	57.0	102.3	164.5	220.1
10	0.1	0.4	0.6	1.0	1.2	7.8	35.3	62.6	97.3	122.6
20	0.0	0.2	0.4	0.5	0.6	4.5	20.4	35.1	52.4	61.7
30	0.0	0.1	0.2	0.2	0.3	2.4	10.5	17.5	24.6	26.9
50	0.0	0.0	0.0	0.0	0.0	0.4	1.5	2.2	2.7	2.7
					Lung Cancer in Male Nonsmokers					
0	0.0	0.0	0.0	0.0	0.2	0.3	1.5	2.9	5.9	18.5
10	0.0	0.0	0.0	0.1	0.2	0.3	1.5	2.9	5.9	15.5
20	0.0	0.0	0.0	0.1	0.1	0.3	1.5	2.9	5.9	12.6
30	0.0	0.0	0.0	0.1	0.1	0.3	1.5	2.9	5.7	9.7
50	0.0	0.0	0.0	0.0	0.0	0.3	1.3	2.2	3.9	4.2

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[a] The 95% confidence limit on the risk values for lung cancer for an unstudied exposure circumstance is a factor of 10. The 95% confidence limit on the risk values for lung cancer on the average determined from 11 unit exposure risk studies is a factor of 2.5. The 95% confidence limit on the risk values for mesothelioma for an unstudied exposure circumstance is a factor of 20. The 95% confidence limit on the risk values for mesothelioma for a studied circumstance can be reasonably averaged as a factor of 5. The values for continuous exposure were derived by multiplying 40 hr/wk risks, obtained from occupational exposures, by 4.2 (the ratio of hours in a week to 40 hours.)

TABLE 6-3. LIFETIME RISKS PER 100,000 PERSONS OF DEATH FROM MESOTHELIOMA AND LUNG CANCER FROM CONTINUOUS ASBESTOS EXPOSURES OF 0.0001 AND 0.01 f/ml ACCORDING TO AGE AND DURATION OF EXPOSURE. U.S. GENERAL POPULATION DEATH RATES WERE USED AND SMOKING HABITS WERE NOT CONSIDERED[a]

	Concentration = 0.0001 f/ml years of exposure					Concentration = 0.01 f/ml years of exposure				
Age at onset of exposure	1	5	10	20	life-time	1	5	10	20	life-time
					Mesothelioma in Females					
0	0.1	0.7	1.2	2.0	2.8	14.6	67.1	120.8	196.0	275.2
10	0.1	0.4	0.8	1.2	1.5	9.4	42.6	75.5	118.7	152.5
20	0.1	0.3	0.4	0.7	0.8	5.6	25.1	43.5	65.7	78.8
30	0.0	0.1	0.2	0.3	0.4	3.1	13.3	22.4	31.9	35.7
50	0.0	0.0	0.0	0.0	0.0	0.6	2.1	3.2	3.9	3.9
					Lung Cancer in Females					
0	0.0	0.0	0.1	0.2	0.5	1.0	4.6	9.2	18.5	52.5
10	0.0	0.0	0.1	0.2	0.4	1.0	4.6	9.2	18.6	43.4
20	0.0	0.0	0.1	0.2	0.3	1.0	4.6	9.2	18.2	34.3
30	0.0	0.0	0.1	0.2	0.3	1.0	4.6	9.0	16.7	25.1
50	0.0	0.0	0.1	0.1	0.1	0.7	3.1	5.5	8.1	8.8
					Mesothelioma in Males					
0	0.1	0.5	0.9	1.5	1.9	11.2	51.0	91.1	145.7	192.8
10	0.1	0.3	0.6	0.8	1.1	7.0	31.2	58.2	84.7	106.8
20	0.0	0.2	0.3	0.4	0.5	4.1	17.5	30.1	44.5	51.7
30	0.0	0.1	0.1	0.2	0.2	2.1	8.8	14.6	20.4	22.3
50	0.0	0.0	0.0	0.0	0.0	0.3	1.1	1.8	2.0	2.1
					Lung Cancer in Males					
0	0.0	0.1	0.3	0.6	1.7	2.9	14.8	29.7	59.2	170.5
10	0.0	0.1	0.3	0.6	1.4	2.9	14.9	29.8	59.5	142.0
20	0.0	0.2	0.3	0.6	1.1	3.1	15.0	30.0	59.4	113.0
30	0.0	0.1	0.3	0.6	0.8	3.1	14.9	29.8	56.6	84.8
50	0.0	0.1	0.2	0.3	0.3	2.5	11.5	20.3	29.1	30.2

[a] The 95% confidence limit on the risk values for lung cancer for an unstudied exposure circumstance is a factor of 10. The 95% confidence limit on the risk values for lung cancer on the average determined from 11 unit exposure risk studies is a factor of 2.5. The 95% confidence limit on the risk values for mesothelioma for an unstudied exposure circumstance is a factor of 20. The 95% confidence limit on the risk values for mesothelioma for a studied circumstance can be reasonably averaged as a factor of 5. The values for continuous exposure were derived by multiplying 40 hr/wk risks, obtained from occupational exposures, by 4.2 (the ratio of hours in a week to 40 hours.)

6-2) and general population (Table 6-3) rates. We are assuming that the current U.S. male mortality rates reflect the experience of 67 percent smokers (many, however, are now ex-smokers) and that current female mortality rates reflect the experience of 33 percent smokers. Using these percentages and the data of Hammond (1966) on the mortality ratio of smokers to nonsmokers, smoking-specific total mortality rates are calculated. Current lung cancer mortality rates for males are multiplied by 1.5 to represent the rates for smoking males. The multiplication factor comes from the fact that the current male rates result from a population where 67 percent of men are smokers or ex-smokers. Correspondingly, current female lung cancer mortality rates are multiplied by 3 to reflect the fact that approximately 33 percent of women are current or ex-smokers. This factor for women may be low, because the current rapid increase in female rates may not yet fully reflect the full impact of women's smoking; however, they should not exceed the male smoker's rates. Nonsmoking lung cancer rates for both males and females are taken from Garfinkel (1981).

The results show the importance of the time course of mesothelioma. Children exposed at younger ages are especially susceptible because of their long life expectancy. The time of exposure plays little role in the lifetime excess risk of lung cancer; any exposure before the age of 45 or 50 contributes equally to the lifetime risk. The risk estimates are uncertain because of the variability of the data from which values of K_L are calculated and from uncertainties in extrapolating from risks estimated at high occupational exposures to concentrations 1/100 and less. Thus, actual risks in a given environmental exposure could be outside the listed ranges.

The risks in tables 6-1, 6-2, and 6-3 would appear to be the best estimates for exposure to fibers released from the variety of asbestos products used in the United States, including products containing small amounts of crocidolite and substantial quantities of amosite. As noted in the tables, the 95 percent confidence limits on the risk estimate for an unstudied exposure circumstance are a factor of times 1/10 and times 10. As indicated in section 3.17, exposures to crocidolite appear to carry a proportionately greater mesothelioma risk. Thus tables 6-1, 6-2, and 6-3 will likely underestimate (by perhaps a factor of 4) the mesothelioma risk to aerosols containing predominantly crocidolite asbestos. Conversely, in some pure chrysotile exposure circumstances (such as in mining and milling), the risk will be overestimated.

6.1.1 Alternative Analyses

As discussed previously, the data strongly support a relative risk model for lung cancer and a linear dose-response relationship. No data indicate the existence of a threshold, although one cannot be ruled out.

If a threshold does exist, there would be a corresponding reduction in the calculated lung cancer risk. There is no evidence of a quadratic term in the dose-response relationship nor is it indicated by existing models for asbestos lung cancer. If, however, a small quadratic term is present, there would be some reduction in the calculated risk.

Alternative models do exist for mesothelioma. There are uncertainties in the power of time at which mesothelioma risk increases. The uncertainty, however, has relatively little effect on calculated lifetime risk values, because a fit must be made to existing occupational risk over a time span of four or five decades, leaving only two or three decades of life for manifestation of different power function effects. A lower power requires a much greater multiplying coefficient. Table 6-4 shows the effect on the calculated lifetime risk of three different time functions that are matched to best fit the time course of risk among insulation workers. Table 6-4 shows that the extremes of effect differ by less than a factor of two. As was shown in Table 3-4, there is very little empirical evidence for quadratic or higher terms in the mesothelioma dose-response relationship, although they are compatible with existing cancer models. If higher than linear terms were present, they would reduce the calculated risks by less than a factor of two.

TABLE 6-4. COMPARISON OF THE EFFECT OF DIFFERENT MODELS FOR THE TIME COURSE OF MESOTHELIOMA RISK FOR A FIVE-YEAR EXPOSURE TO 0.01 F/ML

Age at onset of exposure	Calculated deaths/100,000 males		
	Eq. 3-6	t^5	$t^{3.2}$
0	51.0	76.0	46.0
10	31.2	38.0	27.2
20	17.5	17.5	15.0
30	8.8	7.0	7.0
50	1.1	1.0	1.0

6.2 OBSERVED ENVIRONMENTAL ASBESTOS DISEASE

Asbestos-related disease in persons who have not been directly exposed at the workplace has been reported since 1960. In that year, Wagner et al. (1960) published a review of 47 cases of mesothelioma found in the Northwest Cape Province of South Africa in the previous 5 years. Approximately half of the cases described were in individuals who, decades before, had lived or worked near an area of asbestos mining. The hazard from environmental asbestos exposure was further documented in the findings of Newhouse and Thomson (1965), showing that mesothelioma could occur among individuals whose potential asbestos exposure consisted of having resided near an asbestos factory or in the household of an asbestos worker; 20 of 76 cases from the files of the London Hospital were the result of such exposures.

Of considerable importance are data on the prevalence of X-ray abnormalities and the incidence of mesothelioma in family contacts of amosite factory employees in Paterson, New Jersey. Anderson and Selikoff (1979) showed that 35 percent of 685 family contacts of former asbestos factory workers had abnormalities characteristic of asbestos exposure when they were X-rayed 30 or so years after their first household contact. The data, shown in Tables 6-5 and 6-6, compare the household group with 326 New Jersey urban residents. The overall difference in the percentage of abnormalities between the two groups is highly significant. Of special concern is the finding that the difference in the prevalence of abnormalities in a group of children born into a worker's household after his employment ceased is also significant.

Four mesothelioma cases also occurred among the family contacts of these same factory workers (Anderson et al., 1976). Table 6-7 lists the cases by time from onset of exposure, along with the number of deaths from other causes in the same time period (1961-1977; one death occurred subsequent to 1977). One percent of the deaths after 20 years from first exposure were from mesothelioma; however, further observations will be necessary to fully establish the incidence of this neoplasm among family contacts. An additional contribution of asbestos-related lung cancer could also exist, but studies in this regard have not yet been completed.

A second population-based mortality study of mesothelioma and other cancer risks in environmental circumstances is that of Hammond et al. (1979b). This study compared the mortality of a group of 1779 residents within 0.5 mile of the Paterson amosite asbestos plant with 3771 controls in a different, but

TABLE 6-5. PREVALENCE OF RADIOGRAPHIC ABNORMALITIES ASSOCIATED WITH ASBESTOS EXPOSURE AMONG HOUSEHOLD MEMBERS OF AMOSITE ASBESTOS WORKERS

Exposure group	Total examined	One or more radiographic abnormalities present*	
New Jersey urban residents**	326	15 (5%)	
Entered household after active worker employment ceased†	40	6 (15%)	$\chi^2 = 7.1$ $p < .01$
Household resident during active worker employment†	685	240 (35%)	$\chi^2 = 114$ $p < .001$
Household resident and personal occupational asbestos exposure	51	23 (45%)	

*ILO U/C Pneumoconiosis Classification categories; irregular opacities 1/0 or greater; pleural thickening; pleural calcification; pleural plaques.

**No known direct occupational or household exposure to asbestos.

†No known direct occupational exposure to asbestos.

Source: Anderson and Selikoff (1979).

TABLE 6-6. CHEST X-RAY ABNORMALITIES AMONG 685 HOUSEHOLD CONTACTS OF AMOSITE ASBESTOS WORKERS AND 326 INDIVIDUAL RESIDENTS IN URBAN NEW JERSEY, A MATCHED COMPARISON GROUP

Group	Total examined	Pleural thickening present	Pleural calcification present	Pleural plaques present	Irregular* opacities present
Household contacts of asbestos workers	685	146 (18.8%)	66 (8.5%)	61 (7.9%)	114 (16.6%)
Urban New Jersey residents	326	4 (1.2%)	0 (0.0%)	2 (0.6%)	11 (3.4%)

*ILO U/C Pneumoconiosis Classification irregular opacities 1/0 or greater.

Source: Anderson and Selikoff (1979).

TABLE 6-7. MESOTHELIOMA FOLLOWING ONSET OF FACTORY ASBESTOS EXPOSURE, 1941-1945[a]

Years from onset	Factory workers (933) Total deaths	Factory workers (933) Mesothelioma	Household contacts (2205) Total deaths	Household contacts (2205) Mesothelioma
<20 years	270	0	280	0
20-24 years	102	2	93	0
25-29 years	113	5	111	0
30-34 years	84	7	124	3
35+ years	5	0	56	1
Total >20 years	304	14	384	4
Total all years	574	14	664	4

[a] Data of Selikoff and Anderson.

Source: Nicholson (1981).

economically similar section of town. No differences in the relative mortality experiences are seen, except for one mesothelioma in the neighborhood group. This one case was an electrician; thus, occupational exposure may have contributed to the disease.

6.3 COMPARISON OF OBSERVED MORTALITY WITH EXTRAPOLATED DATA

The mortality data in these two population-based studies can be compared with estimates from the data that led to Table 6-3 but calculated for 35 years, rather than a lifetime. If the air concentration in both circumstances was 200 ng/m^3, approximately 2 mesothelioma deaths/100,000 would be expected in 35 years of observation. In both cases, the exposed population was about 2000; so, the expected number of mesotheliomas would be 0.04 (range: 0.004 to 0.4). The higher numbers observed, particularly in the household group, suggest that higher exposures (e.g., from shaking dusty overalls) may have occurred in workers' homes or that the extrapolations based on occupational data may understate risks.

6.4 COMPARISON OF ESTIMATED MESOTHELIOMAS WITH SEER DATA

The risk estimates of Table 6-1 through 6-3 can also be used to compare estimated mesothelioma risk with that observed in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Cancer Registry Program. Between 1973 and 1978, 170 cases of mesothelioma were identified among females in the SEER program which is based on 10% of the U.S. population (Connelly, 1980). Thus, about 280 cases occur annually in the U.S. among females. Using Equations 3-6d and the current female population of the U.S., it is estimated that 32 cases would occur annually from a continuous lifetime exposure to 0.0001 f/ml (about 3 ng/m^3). However, such a concentration, which was measured in urban areas during 1970-71 would be influenced by the substantial use of asbestos building products. The "background" concentrations during 1910-1940 would likely be less. Nicholson (1983) has estimated that about 20 mesotheliomas would occur among men and women if an average concentration of 2 ng/m^3 existed from 1930.

6.5 LIMITATIONS TO EXTRAPOLATIONS AND ESTIMATIONS

The above calculations of unit risk values for asbestos must be viewed with caution because they are uncertain and are necessarily based on estimates that are subjective, to some extent, because of the following limitations in data: (1) extrapolation from high occupational levels to much lower ambient levels, (2) mass-to-fiber conversion is uncertain, (3) various confounding aspects of the medical data and, very importantly (4) the nonrepresentative nature of the exposure estimates. The ranges of uncertainty estimated may in fact be greater than those stated here, but insufficient information exists by which to make more precise or definite estimates of uncertainty.

7. OTHER REVIEWS OF ASBESTOS HEALTH EFFECTS

7.1 INTRODUCTION

Recently several government agencies in different countries reviewed asbestos health effects. The most important of the reviews outside the United States are those of the Advisory Committee on Asbestos (1979a,b) (ACA) of the British Health and Safety Commission and the report of the Ontario Royal Commission (ORC) (1984). Updates on the British report have been published by Acheson and Gardner (1983), and most recently by Doll and Peto (1985). Each of these major reports was the result of lengthy testimony by many scientists and deliberation by a selected committee over a long period of time. In the United States, the National Academy of Sciences (NAS) has reviewed the non-occupational health risk of asbestiform fibers (National Academy of Sciences, 1984) and a Chronic Hazard Advisory Panel convened by the U.S. Consumer Product Safety Commission (1983) reported on the hazards of asbestos. There are large areas of agreement and some of disagreement between these other reviews and those of this document with regard to the spectrum of asbestos-related disease, the models describing asbestos-related lung cancer and mesothelioma, unit exposure risks in occupational circumstances, possible differences in carcinogenic potency of different asbestos minerals, and risk estimates at low, non-occupational exposures. These are discussed below.

7.2 THE SPECTRUM OF ASBESTOS-RELATED MORTALITY AND FIBER TYPE EFFECTS

There was unanimity that all commercial varieties of asbestos, including chrysotile, crocidolite, amosite, and anthophyllite, produced lung cancer in humans. The Ontario Royal Commission (1984) noted the considerable difference in lung cancer risk in different chrysotile-using processes. The reports implicated chrysotile, crocidolite and amosite in increased risks of mesothelioma. However, they disagreed on the importance of the role of each fiber type. The various British and Canadian reports view chrysotile as being a substantially less potent mesothelial carcinogen than amosite and amosite to be somewhat less potent than crocidolite. In the view of Acheson and Gardner (1983) "exposure to chrysotile alone so far has rarely been shown to cause mesothelioma." The British and Canadian views are based on the high frequency of mesothelioma deaths associated with crocidolite and amosite exposures, even though, in some circumstances, the amphibole usage may have been very small relative to chrysotile. The CPSC report viewed chrysotile as being important in the production of pleural mesothelioma but not for peritoneal tumors. This view is based on similar ratios of pleural mesothelioma to excess lung cancer found among chrysotile-exposed workers compared to mixed or amphibole-exposed workers. The NAS believed that information was insufficient to establish a differential risk based on chemistry. It stated, "many of the apparent differences (in carcinogenic potency) may be explained by the differences in physical properties and concentrations used by the various industries."

All reports noted that the strength of the evidence associating asbestos exposure with cancers other than mesothelioma or of the lung is less. Gastrointestinal and laryngeal cancers were attributed to asbestos exposure by the Ontario Royal Commission (1984) and by the Advisory Committee on Asbestos (1979a,b), although Acheson and Gardner felt in 1983 that the evidence linking asbestos and GI cancer was "less convincing than in 1979." Doll and Peto (1985), in their review, conclude that there are no grounds for believing that gastrointestinal cancers in general are peculiarly likely to be caused by asbestos exposure. They further state that: (1) for laryngeal cancer, on the other hand, the evidence is quite strong; (2) they reserve judgment about the possibility that asbestos causes cancer of the esophagus; and (3) they also note what evidence would be needed to weaken their view regarding possible gastrointestinal tract cancer linkage to asbestos exposure. Both the U.S. Consumer Product Safety Commission Panel (1983) and National Academy of Sciences (1984) noted the increased risk of GI cancers in several cohorts, but each declined to take a firm position on causality. The CPSC Report specifically noted a disagreement on the issue among panelists.

7.3 MODELS FOR LUNG CANCER AND MESOTHELIOMA

All reports adopted models for lung cancer and mesothelioma similar to those of this report, a relative risk model for lung cancer and an absolute risk model for mesothelioma, in which the risk increased as a power function of time from exposure. All noted the limitations on the data establishing a dose-response relationship, but all felt a linear model was most appropriate, particularly for regulatory purposes. None suggested there was any evidence of a threshold for asbestos cancer (although the data were insufficient to exclude one).

7.4 EXTRAPOLATIONS TO LOW EXPOSURE CIRCUMSTANCES

All of the major reviews by government agencies mentioned above undertook quantitative risk assessments for non-occupational or low exposures to asbestos. Because of agreement on the models for lung cancer and mesothelioma, very similar unit risks were estimated. Differences were largely the result of the choice of studies considered and were relatively small. All of the groups recognized the limitations in the data on which extrapolations were based, the dependence of the extrapolation on a linear dose-response relationship, the uncertainties of estimation of asbestos exposure in past years, and the difficulties of converting between different methods of measurement. Two groups (National Academy of Sciences, 1984; U.S. Consumer Product Safety Commission, 1983), estimated risks at lower exposures using average unit exposure risks as was done in this document; the other two (Ontario Royal Commission, 1984; Advisory Committee on Asbestos, 1979a,b) used risk estimates from data in different occupational studies and a range of the results was presented. Various estimates of the uncertainty of these risks were provided; most were of an ad hoc nature. A comparison of these different risk estimates is shown in Table 7-1. There is reasonable agreement between the estimates when consideration is taken of the different exposure circumstances. The NAS value for mesothelioma risk appears to be low relative to their lung cancer risk (the lifetime exposure risk barely exceeds that for lung cancer in a non-smoker). This may be the result of separately choosing b and k in the risk relationship $= bt^k$, rather than determining b after selecting a value for k.

When making the extrapolation from the work place exposure to the ambient exposure, one must be aware that the physical structure and other properties of asbestos may make the exposure risks substantially different.

TABLE 7-1. THE RISKS OF DEATH/100,000 INDIVIDUALS FROM MESOTHELIOMA AND LUNG CANCER FROM A LIFETIME ASBESTOS EXPOSURE TO 0.01 f/ml

Population	Lung cancer	Mesothelioma
	This Document	
Female smokers	150.0 (15 - 1500)	252.0 (12.6 - 5040)
Female nonsmokers	16.4 (1.64 - 164)	272.0 (13.6 - 5440)
Male smokers	238.0 (23.8 - 2380)	181.0 (9.1 - 3620)
Male nonsmokers	18.5 (1.85 - 185)	220.0 (11.0 - 4400)
Males exposed 40 years from age 20 from Table 6-3	88.5 (8.9 - 885)	46.5 (2.3 - 920)
	National Academy of Science (1984)	
Female smokers	57.5 (0 - 275)	22.5 (0 - 875)
Female nonsmokers	7.5 (0 - 32.5)	22.5 (0 - 875)
Male smokers	160.0 (0 - 725)	22.5 (0 - 875)
Male nonsmokers	15.0 (0 - 55)	22.5 (0 - 875)
	U.S. Consumer Product Safety Commission (1983)	
Female smokers	95.2 (30.1 - 301.2)	246.0 (78.0 - 779.9)
Female nonsmokers	15.7 (5.0 - 496)	266.6 (84.3 - 842.9)
Male smokers	155.0 (49.0 - 490.1)	174.2 (55.1 - 551.0)
Male nonsmokers	17.5 (5.54 - 55.4)	215.3 (68.1 - 680.8)
	Ontario Royal Commission[a] (1984)	
A hypothetical workforce of 385 male smokers, 385 male nonsmokers, 115 female smokers, and 115 female nonsmokers	0.4 - 76	1.4 - 187.5
	Advisory Committee on Asbestos[b] (1979a,b)	
Males and females	8.6 - 286	
	Doll and Peto (1985)[c]	
Males	25.2	5.6

[a] Exposure of 25 years from age twenty-two.

[b] 50 years exposure.

[c] Exposure of 35 years from age 20.

7.5 RELATIVE CARCINOGENICITY OF DIFFERENT FIBER TYPES

As briefly mentioned above, some differences exist among the major reports by different national organizations on the relative carcinogenicity of different asbestos fiber types. The view of the British in the Report of the Advisory Committee on Asbestos (1979a,b) and of Acheson and Gardner (1983), who wrote the background health effects paper and a 1983 update, is that crocidolite is a very potent mesothelial carcinogen, amosite is less so, and chrysotile rarely produces such a tumor. Their view is based on data similar to that of Table 3-35 and on the finding that in surveys of individuals with mesothelioma, particularly in Great Britain, an exposure to crocidolite or amphiboles can usually be documented either in a history or in analysis of lung tissue for asbestos fibers (a history of exposure to chrysotile is equally common). It is not certain how much weight one should place upon this latter evidence. In Great Britain, as in the United States, occupational exposure to asbestos largely involves exposure to mixtures of fibers. Thus, an association between amphibole exposure and mesothelioma would be expected. It is found that amphibole asbestos varieties are retained in the lung for decades after exposure, whereas chrysotile undergoes removal processes of various types. Thus, with even brief or low intensity amphibole exposures, fibers are commonly found in lung tissue analysis.

The Ontario Royal Commission (1984) also noted that there is a convincing case against amphiboles in relation to the incidence of mesothelioma and that, while chrysotile is capable of causing mesothelioma in humans, the incidence among chrysotile-exposed cohorts has been relatively low. For this, they cite the example of the Charleston, South Carolina textile plant with an extraordinarily high incidence of lung cancer, but only one mesothelioma.

Doll and Peto (1985) state that, in their opinion, the epidemiological data show that chrysotile can cause both mesothelioma and lung cancer but that peritoneal mesothelioma is rarely caused by chrysotile exposure and that crocidolite and amosite are more dangerous then chrysotile when used in the same way. Doll and Peto (1985) particularly noted the much greater mesothelioma risk in the experience of gas mask manufacturing workers who used crocidolite compared to those who used chrysotile (Acheson et al., 1982). However, no exposure data were available.

The view of the National Academy of Sciences (1984) report was that the epidemiological literature on the relative ability of different fiber types to cause disease does not present a clear picture. The observed variation in risk may be due to different effects caused by different fiber types or dimensions used in processes in which other contaminants are present. They state that the magnitude of the difference in reported risks is not likely to be explained by fiber or process differences alone.

7.6 NON-MALIGNANT EFFECTS

All reviews of asbestos did not consider a non-malignant disease to be of importance at the exposures found in environmental circumstances. For example, the Ontario Royal Commission (1984) concluded that "at low levels of occupational exposure to asbestos the fibrotic process in the lungs, if indeed it can be initiated, will not likely progress to the point of clinical manifestation or even the mildest discomfort. On the basis of the available data our best judgement as to the lifetime occupational exposure to asbestos at which the fibrotic process cannot advance to the point of clinical manifestation of asbestosis is in the range of 25 f-y/mℓ and below."

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